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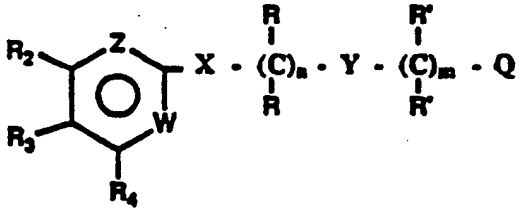

(I)

(57) Abstract

This invention relates to compounds having selective LTB_4 antagonist properties and comprising an aryl or heteroaryl mono- or bicyclic ring which has at least two substituents attached thereto; (1) a substituted or unsubstituted aryl or heteroaryl mono- or bicyclic ring and (2) a substituent chain having a terminal carboxylic acid functional group or derivative thereof attached thereto. This invention further relates to processes for their preparation and therapeutic compositions comprising said compound and methods for the treatment of disorders involving LTB_4 agonist-mediated activity utilizing said compositions wherein the compounds are described by general formula (I) and pharmaceutically acceptable salts thereof.

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SUBSTITUTED BICYCLIC BIS-ARYL COMPOUNDS EXHIBITING SELECTIVE LEUKOTRIENE B_4 ANTAGONIST ACTIVITY,THEIR PREPARATION AND USE IN PHARMACEUTICAL COMPOSITIONS

Field of the Invention

The present invention relates to a class of novel compounds useful in the treatment of a variety of diseases that involve undesirable inflammatory or hypersensitivity responses in diverse animal tissues. Approaches to the treatment of these diseases have been as varied as the tissues in which such responses take place, and include the administration of antihistamines, analgesics such as aspirin, topical coal tar as well as others.

A more recent approach to the moderation of inflammatory and hypersensitivity responses has focused on blocking the action of arachidonic acid metabolites (including the prostaglandins), lipoxygenases and the leukotrienes. The leukotrienes (LT) metabolites are formed by oxygenation of a lipoxygenase (5-hydroperoxy-tetraenoic acid (5-HPETE)) which is formed by the specific oxygenation of the C-5 position of arachidonic acid. The first leukotriene formed in the metabolic pathway is the unstable epoxide intermediate leukotriene A_4 (LTA_4) which is the precursor to the family of peptido-leukotrienes, the first in the pathway being LTC_4 which is formed by glutathione addition. LTC_4 is transformed subsequently into LTD_4 and LTE_4 by successive elimination of a glutamyl and glycine residue. The peptido-leukotrienes primarily act on smooth muscle and other cells having contractile capacity, as well as playing a key role in hypersensitivity reactions. In addition, the peptido-leukotrienes are spasmogens, increase vascular permeability, activate airway smooth muscle, stimulate mucous secretion and are involved with the pathogenesis of certain inflammatory diseases such as bronchitis, ectopic and atopic eczema and psoriasis. Leukotrienes appear to be involved in the pathogenesis of asthma such as allergic pulmonary disorders of asthma,

hay fever and allergic rhinitis. In addition, LTC_4, LTD_4 and LTE_4 may also decrease blood pressure by an action on the heart, because they reduce myocardial contractility and coronary blood flow.

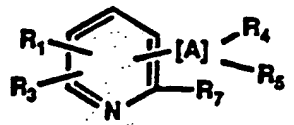
Another family of leukotrienes, LTB_4, is derived from LTA_4 by hydrolase-catalyzed addition of water. This 5,12-dihydroxy derivative causes adhesion and chemotactic movement of leukocytes, stimulates aggregation, enzyme release and generation of superoxide in neutrophils. Additionally, LTB4 is a potent chemotactic and chemokinetic agent for eosinophils, macrophages and monocytes, stimulates suppressor T lymphocytes and enhances natural cytotoxic cell activity. LTB_4 is also a potent (indirect) bronchoconstrictor but in contrast to the peptido-leukotrienes C_4, D_4 and E_4 does not appreciably stimulate mucous production and induce edema of the airways by increasing vascular permeability.

It has been suggested that compounds antagonizing LTB_4 activity may be valuable in the treatment of inflammatory diseases caused by tissue degrading enzymes and reactive chemicals liberated by tissue-infiltrating and aggregating polymorphonuclear leukocytes. Such disease states include inflammatory bowel disease, reperfusion injury, chronic lung diseases, various arthritic conditions, inflammatory conditions associated with asthma (such as late phase hypersensitivity) and psoriasis.

Reported Developments

Compounds reported to have anti-inflammatory properties and/or heterocyclic structures relevant to those within the scope of the present invention are described below.

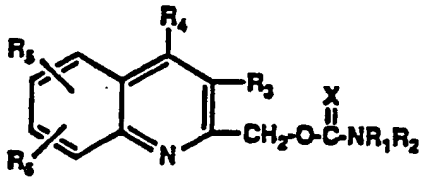
In the Belgian Patent 724,667 pyridine derivatives of structure:



wherein R_1 is a hydrogen atom or among others a phenyl, R_3 is hydrogen or an alkyl, R_4 and R_5 are in particular hydrogen, an alkyl or a phenyl, R_7 is a radical of structure $-OR_8$ or $-SR_8$ for which R_8 is in particular a lower alkyl

optionally substituted by a nitro, an amino or a halogen, or a benzyl, and [A] is a heterocyclic or carbocyclic aryl. These products are useful in the area of anti-inflammatory agents.

In US Patent 3,391,146, there are disclosed anti-inflammatory agents of general formula:



wherein X is O or S, R_1 and R_2 are among others a lower alkyl, R_3, R_4, R_5 and R_6 are among others alkoxy, alkylthio or phenyl radicals.

A variety of compounds exhibiting leukotriene B_4 antagonist activity have been reported. These include compounds having chemical structures mimicking leukotriene structures such as Sumitomo's SM 9064, UpJohn's U-75360 and U-75302 and Ciba Geigy's CGS 23113. Other compounds, some of which include monocyclic ring structures and are disclosed in EP 276064, EP 276065 and EP 292977, are reported to exhibit both LTD_4 and LTB_4 antagonist properties.

The following publications disclose compounds related to those of the present invention but are neither disclosed herein nor are they disclosed for use for the purposes disclosed herein.

EP Publication No. 0090353 discloses pyridon-2 derivatives which have a 2-3 atom side chain having an ester group thereon and substitution of a 2- or 3-thienyl ring at the 6-position. These compounds are antiphlogistic agents.

EP Publication No. 0210084 discloses that bicyclic aryl and N-heteroaryl di- substituted amides are useful as anxiolytic agents.

JP Kokai Tokkyo Koho JP 82 58,666 discloses that pydidine and pyrimidine compounds having a thioalkyl side carboxy chain are anti-ulcer agents.

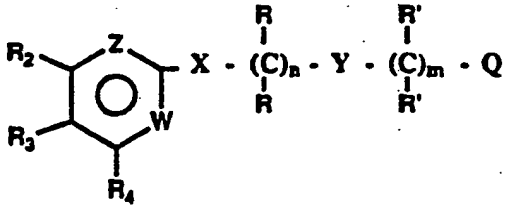
PCT International Publication No. WO89/11279 discloses nucleic acid interacting unfused heteropolycyclic compounds which inhibit translation and interfering with viral replication processes such as the replication of HIV.

The present invention is directed to a class of novel substituted bis-aryl and/or heteroaryl mono and/or bicyclic ring containing compounds which exhibit selective LTB_4 antagonist activity.

Summary of the Invention

This invention relates to compounds having selective LTB_4 antagonist properties and comprising an aryl or heteroaryl mono- or bicyclic ring which has at least two substituents attached thereto; (1) a substituted or unsubstituted aryl or heteroaryl mono- or bicyclic ring and (2) a substituent chain having a terminal carboxylic acid functional group or derivative thereof attached thereto. This invention further relates to processes for their preparation and therapeutic compositions comprising said compound and methods for the treatment of disorders involving LTB_4 agonist-mediated activity utilizing said compositions.

More specifically the compounds of this invention are described by Formula I:



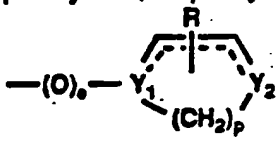
Formula I

where

m is 1-8, n is 0-8 and n+m is 2-8;

X is S, O, NR", CR'R', CR'=CR', CO-NR", NR"-CO or a bond;

Y is S, O, NR", CR'R', CR'=CR', CO-NR", NR"-CO, CO, CR'-OH, phenylene, naphthylene or a nitrogen-containing cyclene group of the formula



where Y_1 and Y_2 are independently CR' or N, p is 1-3, e is 0 or 1 and e is 0 when Y_1 is N;

W and Z are independently CR' or N provided that when both W and Z are N then n+m is 2-7;

R and R' are independently R_1 or R_1-loweralkyl- or vicinal R and/or R' groups together or vicinal R' and R" groups together may be $-(CH_2)_y-$ where y is 2-4, thus forming a 4-6 membered ring and geminal R and/or R' groups may together form a spiro substituent, $-CH_2-(CH_2)_z-CH_2-$ where z is 0-4 or an alkylidenyl substituent, $=CHR_5$, where R_5 is hydrogen or alkyl;

R" also may be hydrogen, alkyl or aralkyl;

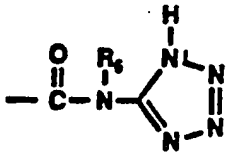
R_1 is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, aryl, hydroxy, alkoxy, aryloxy, aralkoxy, acyl, halo, amino, mono- and dialkylamino, aralkylamino, acylamino, carboxy, carbalkoxy, carbamyl or mono- and dialkylcarbamyl;

R_2, R_3 and R_4 are independently R_1, R_1-loweralkyl- or an optionally substituted mono- or bicyclic aryl or heteroaryl group containing about 5 to about 12 atoms wherein each ring comprising said group contains 0-2 hetero atoms selected from N, O or S provided said hetero atoms are not vicinal oxygen and/or sulfur atoms, and provided further that at least one of R_2, R_3 and R_4 is said aryl or heteroaryl group;

R_2, and R_3 or R_3 and R_4 together with the ring to which they are attached may form an optionally substituted fused bicyclic [5,6], [6,6] or [7,6] ring system which may contain from 0-2 hetero atoms in each ring selected from N, O and S, provided said hetero atoms are not vicinal oxygen and/or sulfur atoms;

R_4 also may be $X_1-(CH_2)_t-R_3$ provided that R_3 is said mono- or bicyclic aryl ring system, X_1 is S, O, NR", CR'R' or CO and t is 1-4; and

Q is $COOR_6$, COOM, $CONR_7R_7$, CN, $CONHSO_2R_6$, tetrazolyl or tetrazolyl substituted with alkyl, carboxyalkyl or carbalkoxyalkyl, and



, where R_6 is hydrogen, alkyl or aralkyl, R_7 is hydrogen,

alkyl, aralkyl or cycloalkyl, M is a metal or ammonia salt and R_7 and R_7 together form a 3-6 membered ring provided that R_7 is hydrogen when R_2 and R_3 together and R_3 and R_4 together form a fused ring;

and pharmaceutically acceptable salts thereof.

Detailed Description and Preferred Embodiments

As employed above and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Bicyclic aryl" means a bicyclic ring system composed of two fused rings which may be partially or completely unsaturated carbocyclic and/or heterocyclic rings. More specifically, the bicyclic 6,6; 6,5; and 6,7 aryl ring systems are preferred and include naphthalene, quinazolines, benzazepines, quinoline, isoquinoline, and purine.

"Monocyclic aryl" means a partially or completely unsaturated carbocyclic or heterocyclic ring. Preferred monocycles include benzene, thiophene, pyridine, furan and pyrimidine.

"Aryl" refers to a partially or completely unsaturated carbocyclic or heterocyclic aromatic ring.

"Alkyl", either alone or with various substituents defined herein, means a saturated aliphatic hydrocarbon, either branched- or straight-chained. A "loweralkyl" is preferred having about 1 to about 6 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, butyl, sec-butyl, t-butyl, amyl and hexyl.

"Alkoxy" refers to a loweralkyl-O-group.

"Alkenyl" refers to a hydrocarbon having at least one point of unsaturation and may be branched- or straight-chained. Preferred alkenyl groups have 2 to about 6 carbon atoms present. Exemplary alkenyl groups include vinyl, allyl, ethynyl and isopropenyl.

The preferred aryloxy group is phenoxy.

"Aralkyl" means an alkyl group substituted by an aryl radical. The preferred aralkyl groups are benzyl or phenethyl.

The preferred aralkoxy groups are benzyloxy and phenethoxy.

"Halo" means a halogen. Preferred halogens include chloride, bromide and fluoride. The preferred haloalkyl group is trifluoromethyl.

Still more specifically, this invention may be described according to Formula I above by the following preferred embodiments (A) - (H):

(A) where m is 1 and n is 1-7;

X is S or O;

Y is O or CH_2;

Z is N and W is CR';

R and R' are independently hydrogen or alkyl;

R_2 and R_4 are independently hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group;

R_3 is hydrogen or together with R_2 may form a fused benzene ring which may further be substituted with halo, alkyl or alkoxy; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 is hydrogen or alkyl and R_7 is hydrogen.

(B) where m is 2-7 and n is 0;

X is a bond;

Y is S or O;

W and Z are N;

R is hydrogen;

R' is independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2 and where R_1 is hydrogen, alkyl, aralkyl, aryl or halo;

R_2, R_3 and R_4 are independently hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents

independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, methylenedioxy, ethylenedioxy, aminomethyleneoxy, aminovinylene, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, ureodo, trifluoroacetamido or benzamido or an aryl group selected from imidazol, thiazol or pyridyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2, R_3 and R_4 is said aryl group;

R_3 is hydrogen or alkyl or together with R_2 may form a fused benzene ring which may further be substituted with halo, alkyl or alkoxy; and

Q is $COOR_6$, COONa, $CONR_7R_7$ or tetrazolyl where R_6 is hydrogen or alkyl and R_7 is hydrogen.

(C) where m is 2-7 and n is 0

X is a bond;

Y is S or O;

Z is N and W is CR';

R is hydrogen;

R' is independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2 and where R_1 is hydrogen, alkyl, aralkyl, aryl or halo;

R_2, R_3 and R_4 are independently hydrogen, alkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, methylenedioxy, ethylenedioxy, aminoethylene, aminomethyleneoxy, aminovinylene, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, ureido, trifluoroacetamido or benzamido or an aryl group selected from imidazol, thiazol or pyridyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2, R_3 and R_4 is said aryl group and more than one said aryl groups are ortho to each other; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

(D) where m is 2-7 and n is 0;

X is S or O;

Y is a bond;
Z is N and W is CR';
R is hydrogen;
R' is independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2 and R_1 is hydrogen, alkyl, aralkyl, aryl or halo;
R_2, R_3 and R_4 are independently hydrogen, R' or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2, R_3 and R_4 is said aryl group; and
Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

(E) where n is 0-4, m is 1-5 and n+m 2-6;
X is S, O, CR'=CR' or CHR'-O;
Y is phenyl or a heterocyclic ring of the formula
where Y_1 and Y_2 are independently CR' or N and p is 1-3;
Z is N and W is CR';
R and R' are independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2;
R_1 is hydrogen, alkyl, aralkyl, aryl or halo;
R_2 is hydrogen, cycloalkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;
R_3 is hydrogen;
R_4 is hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido; provided at least one of R_2 and R_4 is said aryl group; and
Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

(F) where m is 1-4 and n is 1-5;
X is S or O;
Y is CO-NR", NR"-CO, CO or CR'OH;
Z is N and W is CR';

R is hydrogen;

R' is independently hydrogen, or $(CH_2)_x$-R_1, where x is 0-2;

R" is hydrogen, alkyl or aralkyl;

R_1 is hydrogen, alkyl, aralkyl, aryl or halo;

R_2 is hydrogen, alkyl,cycloalkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;

R_3 is hydrogen;

R_4 is hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

(G) where m+n=2-7;

X is S, O, CR'R' or CR'=CR';

Y is CR'R';

Z and W are CR';

R is independently hydrogen or alkyl;

R' is independently hydrogen, alkyl, aralkyl, aryl or halo;

R_2, is hydrogen, alkyl,cycloalkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;

R_3 is hydrogen or alkyl;

R_2 and R_3 together may form a fused benzene ring which may be substituted with a substituted or unsubstituted R_1 mono- or bicyclic aryl ring and/or further substituted with halo, alkyl, alkoxy or aralkoxy;

R_4 is hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group; and

It is essential that the aryl ring described by Formula I has attached thereon at least one of the second aryl function groups. This may be attached as in Formula I as at least one of R_2, R_3 and R_4 or when R_2 and R_3 together or R_3 and R_4 together are a fused ring it may be attached to the formed fused ring. This second aryl function may be optionally substituted by alkyl, alkoxy, hydroxy, methylenedioxy, halo, haloalkyl, thio, alkylthio, nitro, amino, mono- and dialkylamino, cycloalkylamino, acetamido, trifluoroacetamido, benzamido, carboxy, carbalkoxy, carbaralkoxy, carbamyl, mono- and dialkylcarbamyl or arylcarbamyl.

The preferred position for the attachment of the second aryl function is meta to the chain having a terminal carboxylic acid functional group or derivative.

Among the most preferred chains having a terminal carboxylic acid functional group are:

$-(CH_2)_{m+n}-CR'R'-Q$ where m+n is 3-7,

$-(CH_2)_n-CH=CH-(CH_2)_m-CR'R'-Q$ where m+n is 1-5,

$-O-(CH_2)_{m+n}-CR'R'-Q$ where m+n is 3-7,

$-O-(CH_2)_n-CH=CH-(CH_2)_m-CR'R'-Q$ where m+n is 1-5; and

where R' is hydrogen or lower alkyl and Q is tetrazolyl, $-COOR_6$ where R_6 is hydrogen or alkyl, COOM or $CONR_7R_7$ where M is an alkali metal, R_7 is hydrogen or alkyl, or R_7 and R_7 together with the nitrogen to which they are attached form a 5-6 membered nitrogen-containing ring.

In addition to the two substituents attached to the aryl or heteroaryl mono- or bicyclic ring system as described above, it is often desirable to have a third substituent present. This may be the same or different as these already present in the molecule. It is preferred that such third substituent also be one described above as a second aryl substituent. This may be the same or different as that already present and it is further preferred that such substituent also be in the meta position to the acid chain function. In those formulae where Z and/or W are nitrogen, it is preferred that both R_2 and R_4 are a second aryl function.

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 is hydrogen or alkyl.and R_7 is hydrogen.

(H) where m+n=2-7;

X is S, O, CR'R' or CR'=CR';

Y is CR'R';

Z is N or CR' and W is CR';

R is hydrogen;

R' is independently hydrogen, alkyl, aralkyl, aryl or halo;

R" is hydrogen or alkyl;

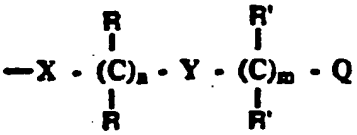
R_2 hydrogen, alkyl, cycloalkyl halo or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;

R_3 hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group;

R_4 is X_1-$(CH_2)_q$-R_3 where X_1 is O, NR", CR'R' or CO and q is 1-4; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

Turning now to the two substituents which are attached to the aryl or heteroaryl mono- or bicyclic ring system described by Formula I. The preferred first substituent is a substituted or unsubstituted aryl or heteroaryl mono- or bicyclic ring and which will be referred to in this case as the second aryl function. The preferred second substituent is a chain having a terminal carboxylic acid functional group or derivative thereof which is described by



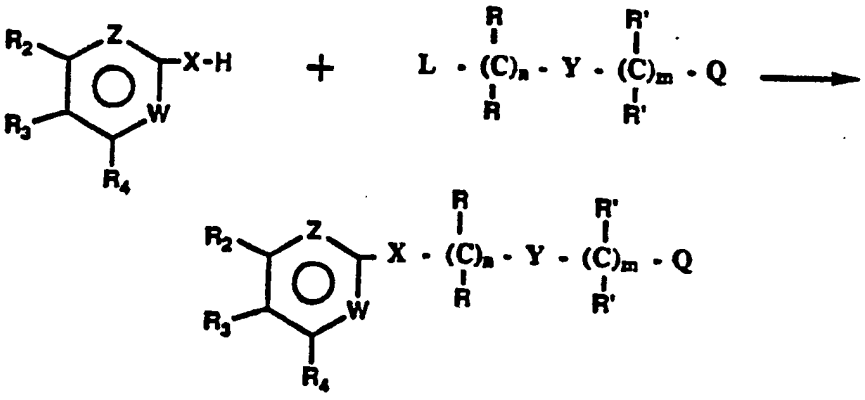
where X, Y, Q, R, R', n and m are as described above.

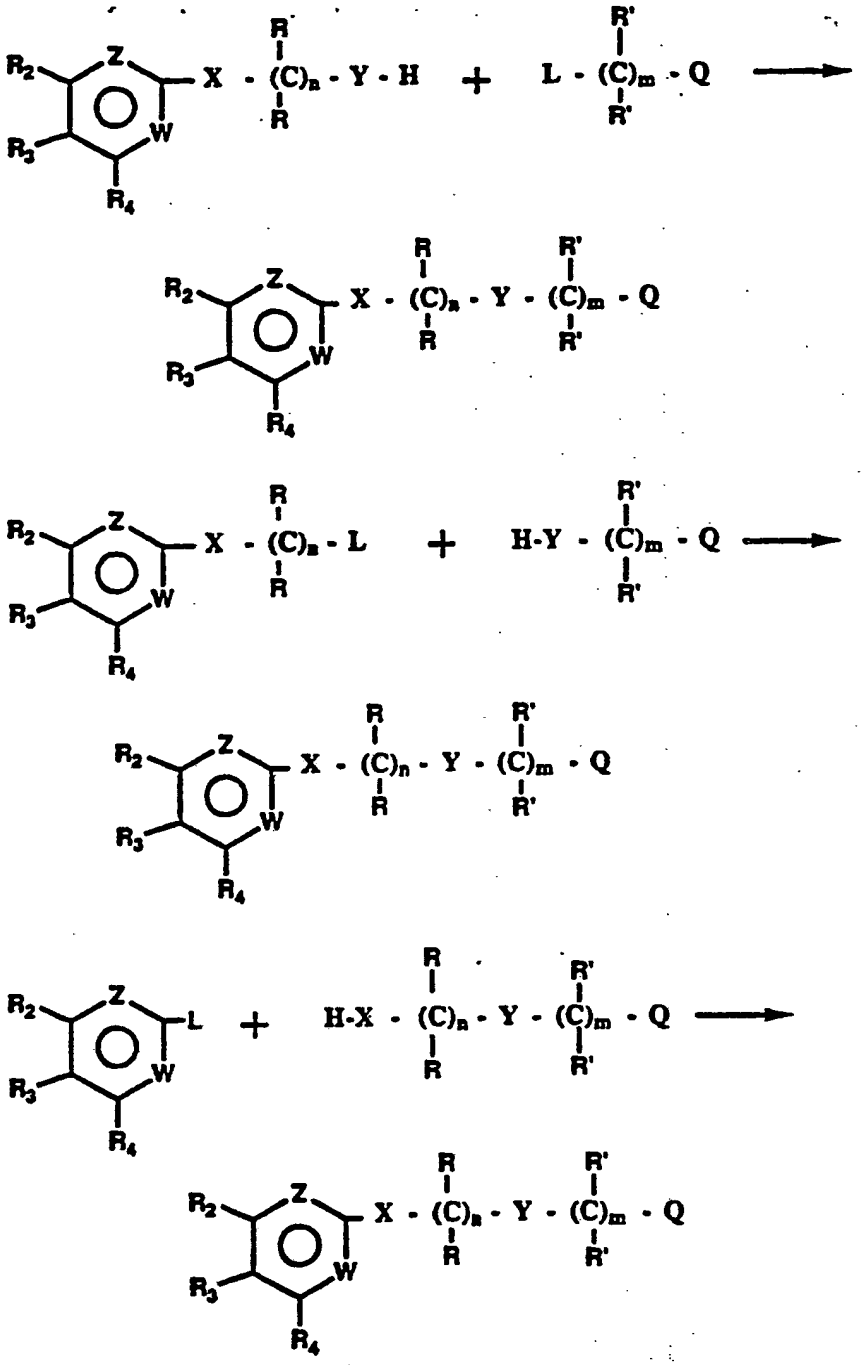
The compounds of this invention may be prepared by employing art recognized procedures from known compounds or readily preparable intermediates. Exemplary general procedures are as follows:

Since the compounds of this invention have at least two substituents which are present, the introduction of each substituent to the aryl ring system is, of course, dependent on the specific substituents involved and the chemistry necessary for their formation. Thus, consideration of how one substituent would be affected by a chemical reaction when forming a second substituent would involve techniques familiar to the skilled artisan. This would further be dependent on the bicyclic ring system involved.

It is convenient to synthesize these molecules by employing condensation reactions at reactive X and Y sites of the molecule. Exemplary general procedures are as follows and are basic to developing the molecules having the required substituents present. The substitution patterns for each of the mono- and bicyclic rings would depend on the chemistry of the particular ring. Any such adjustments to the chemistry would be familiar to one skilled in the art.

Thus, in order to prepare those compounds where X or Y is O, S or NR' the following reactions or combination of reactions may be employed:





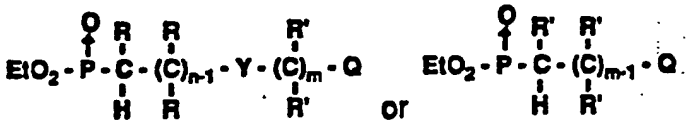
When X or Y is O or S, the compounds may be prepared by condensation of an aryl or heteroaryl alcohol or thiol with a compound of the formulae L - $(CRR)_n$ - Y - $(CR'R')_m$ - Q or L - $(CR'R')_m$ - Q where Q is preferably a nitrile, ester or tetrazole and L is a leaving group such as halo (preferably bromo), tosylate or mesylate.

The reaction is generally carried out in the presence of any basic medium normally employed to deprotonate an alcohol or thiol, in particular an alkaline alcoholate, an alkaline hydride, or a carbonate (for example potassium tertbutylate, sodium ethylate, sodium hydride, sodium hydroxide, triethylamine, silver carbonate, potassium carbonate, sodium carbonate, diisopropyl/ethylamine or methyl magnesium halides.), in an organic solvent such as an alcohol (for example ethanol, i-propanol, etc.), an aromatic hydrocarbon (for example toluene), an amide (for example dimethylformamide) or an oxide (for example dimethyl sulphoxide), at a temperature of between 30 minutes to 96 hours depending on the substituents present. The reaction is usually carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to diethyl ether, THF, N,N-dimethylformamide, dimethyl-sulfoxide, dioxane and the like.

It is understood that when R_1, R_2, R_3 and R_4 carry an amino or alkylamino radical, or when a product of general formula I for which Q is a 5-tetrazolyl radical is allowed to react, it is necessary to protect the amino radicals by any method which does not modify the rest of the molecule. The protection is carried out by any known method for the protection of amines and in which the introduction of the radical and its removal does not affect the rest of the molecule. In particular, there are used the methods described by T.W. Greene, Protective Groups in Organic Synthesis, A. Wiley - Interscience Publication (1981), or by Mc Omie, Protective Groups in Organic Chemistry. By way of example, the protective radicals may be chosen from among methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, allyloxycarbonyl, vinyloxycarbonyl, benzyloxycarbonyl or its substituted derivatives, trichloroethoxycarbonyl, formyl, acetyl, trichloroacetyl, trifluoroacetyl, chloroacetyl, trityl, benzhydryl, benzyl or allyl.

When X is an alkyl group, it is convenient to prepare these compounds by Friedel-Crafts alkylation or by the Wittig reaction followed by reduction.

Those compounds where X and/or Y are CR'=CR' are prepared by reacting the appropriate aldehyde or ketone with an appropriate Wittig reagent or modified Wittig reagent of the formula



where Q is cyano or carbalkoxy.

Reference for the Wittig reaction and modified Wittig reaction to control the formation of the trans and cis configuration at the double bond and the isomerization of cis and trans isomers can be found in A. Maercher, Organic Reactions, 14, 270,1965.

The intermediate aldehyde compounds may be prepared in the usual manner from the corresponding carboxylic acid with an alkylithium reagent, or from the oxidation of the corresponding alcohol. The aldehyde can also be obtained by Friedel-Crafts acylation or formylation ($POCl_3$/DMF).

When X and/or Y are NR"–CO or CO–NR" then the condensation of an acid or an acid halide with the appropriate aryl amine will give the desired compound.

When it is desired to prepare a product for which Q is a carboxy radical, condensation is carried out on the ester and then converted to an acid. Hydrolysis of the ester is carried out according to the usual methods, in particular in basic medium by the action of an alkaline base such as sodium hydroxide or potassium hydroxide, in alcoholic or hydroalcoholic solution (for example in ethanol-water or methanol-water medium), at a temperature of between 20°C and the reflux temperature of the reaction mixture. It is also possible to carry out the reaction in the presence of a lithium halide in collidine, preferably under inert atmosphere, at the reflux temperature of the reaction mixture.

When it is desired to obtain a product for which Q is an alkoxy-carbonyl radical, the acid obtained is converted to an ester. The reaction is carried out in a basic medium, for example in the presence of a base such as an alkaline alcoholate, an alkaline hydride or a carbonate in an organic solvent such as an alcohol (for example ethanol, i.propanol), an amide (for example dimethyl-formamide), an aromatic hydrocarbon (for example toluene), or an oxide (dimethyl sulphoxide), at a temperature of between 50 and 120°C.

Conversion of the nitrile to an acid is carried out by acid or basic hydrolysis, for example by sulphuric acid in aqueous medium, at the reflux temperature of the reaction mixture or by potassium hydroxide in aqueous or hydro-alcoholic medium, at the reflux temperature of the reaction mixture.

Conversion of the nitrile to a 5-tetrazolyl radical is carried out by treating an alkaline nitride for example sodium nitride. The reaction is carried out in the presence of ammonium chloride in an organic solvent such as an amide (for example dimethylformamide, dimethylacetamide), at a temperature of between 80 and 150°C.

Conversion of the nitrile into an amide is carried out by hydration in acid medium, for example by treating in formic acid/hydrochloric acid medium, at a temperature of about 20°C.

The tetrazoles may be formed from the nitrile at various stages of the synthesis by treating an alkaline nitride for example sodium nitride. The reaction is carried out in the presence of ammonium chloride in an organic solvent such as an amide (for example dimethylformamide, dimethylacetamide), at a temperature of between 80 and 150°C. The tetrazoles may also be formed with hydrazoic acid formed in situ from sodium azide and an acid.

Various substituents on the present new compounds, e.g., as defined in R_1 and substitution on the aryl or heteroaryl rings of R_1, R_2 or R_3 or where R_2 and R_3 together or R_3 and R_4 together, can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by known methods of substitution or conversion reactions. If the substituents themselves are reactive, then the substituents can themselves be protected according to the techniques known in the art. A variety of protecting groups known in the art, may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis" by T. W. Green, John Wiley and Sons, 1981. For example, nitro groups can be added by nitration and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement of the diazo group. Acyl groups can be added by

Friedel-Crafts acylation. The acyl groups can then by transformed to the corresponding alkyl groups by various methods, including the Wolff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono- and di-alkylamino groups; and mercapto and hydroxy groups can be alkylated to form corresponding ethers. Primary alcohols can be oxidized by oxidizing agents known in the art to form carboxylic acids or aldehydes, and secondary alcohols can be oxidized to form ketones. Thus, substitution or alteration reactions can be employed to provide a variety of substituents throughout the molecule of the starting material, intermediates, or the final product.

More specifically, when it is desired to obtain a product which contains an amino substituent this may be obtained from the corresponding nitro derivative by any known method for reducing a nitro radical without affecting the rest of the molecule. The reaction is advantageously carried out by reducing with stannous chloride, in an organic solvent such as an alcohol, for example ethanol, at the reflux temperature of the reaction mixture.

According to the invention, the products of general formula I which contain a mono- or dialkylamino, benzoylamino or trifluoroacetamido substituent may also be obtained from the corresponding derivative which bears an amino substituent, by any known method for alkylating or acylating an amine without affecting the rest of the molecule. The alkylating reaction may be implemented by the action of ethyl orthoformate or the corresponding carbonyl derivative, in acid or neutral medium, followed by reduction for example by sodium borohydride.The acylating reaction is carried out in particular by the action of a reactive derivative of the acid, for example the acid chloride, the anhydride, a mixed anhydride or a reactive ester, in an organic solvent such as a chlorinated solvent (for example dichloromethane, dichloroethane, chloroform), an amide (for example dimethylacetamide, dimethylformamide), in the presence of an acid acceptor such as an azotized organic base (for example triethylamine, dimethylaminopyridine, N-methylmorpholine), at a temperature of between -40 and +40°C.The reaction is carried out in an organic solvent such as for example toluene at the reflux temperature of the reaction mixture.

The starting materials for this invention are either known or can be prepared by known processes in the art. For example, the thioalcohols may be prepared by the action of phosphorus pentasulphide on the corresponding hydroxyl derivative followed by the condensation reaction as above.

The heterocyclic alcohol starting materials may be prepared by the action of an α-ethylenic ketone of general formula $R_2CO-CH=CHR_4$ wherein R_1 and R_4 are as previously defined, on an N-carbamoylmethylpyridinium salt [prepared according to the method described by O. ALBRECHT et al., Helv. Chim. Acta 24, 241E (1941)], in the presence of a base such as for example sodium hydroxide, followed by treatment in acid medium, at a temperature of about 20°C.

The heterocyclic alcohol starting materials where R_2 forms with R_3 a benzene ring, optionally substituted, may be prepared from a substituted ketoamide of general formula $R_4-CO-CH_2-CONH-Ph$, wherein R_4 is as previously defined and substitution therein may be halogen, alkyl or alkoxy radical, by treating in acid medium. The reaction may be carried out in sulphuric acid, preferably aqueous sulfuric acid, at a temperature of about 100°C.

Other starting materials which are nitriles or alcohols may be prepared by analogous methods described for the preparation of products according to the invention.

The products according to the invention may be purified by known physical methods such as crystallization, distillation or chromatography.

Certain compounds of this invention may have at least one asymmetric carbon atom such as those compounds having different geminal R or R' groups. Further, certain compounds of this invention may exist in their cis or trans configuration such as those compounds where X and/or Y is CR'=CR'. As a result, those compounds of this invention may be obtained either as racemic mixtures, diastereoisomeric mixtures or as individual enantiomers. The product may be synthesized as a mixture of the isomers and then the desired isomer separated by conventional techniques such as chromatography or fractional crystallization from which each diastereomer may be resolved. On

the other hand, synthesis may be carried out by known stereospecific processes using the desired form of the intermediate which would result in obtaining the desired stereospecificity.

Reference to the separation of cis and trans isomers by chromatography may be found in W. K. Chan, et al, J. Am. Chem. Soc. 96, 3642, 1974.

It is to be understood that the scope of this invention encompasses not only the various isomers which may exist but also the various mixture of isomers which may be formed. The resolution of the compounds of this invention and their starting materials may be carried out by known procedures. Incorporation by reference is hereby made to the four volume compendium Optical Resolution Procedures for Chemical Compounds: Optical Resolution Information Center, Manhattan College, Riverdale, New York. Such procedures are useful in the practive of this invention. A further useful reference is Enantiomers, Racemates and Resolutions: Jean Jacques, Andre Collet and Samuel H. Wilen; John Wiley & Sons, Inc., New York, 1981. Basically, the resolution of the compounds is based on the differences in the physical properties of diastereomers. Conversion of the racemates into a mixture of diastereomers by attachment of an enantiomerically pure moiety results in forms that are separable by fractional crystallization, distillation or chromatography.

The present compounds form salts with acids when a basic amino function is present and salts with bases when an acid function, i.e., carboxyl, is present. All such salts are useful in the isolation and/or purification of the new products. Of particular value are the pharmaceutically acceptable salts with both acids and bases.

When Q represents a carboxy radical, the products according to the present invention may be converted to metal salts or to addition salts with an azotized base, according to methods known per se. These salts may be obtained by the action of a metallic base (for example an alkali metal or alkaline-earth metal base), of ammonia or of an amine, on a product according to the invention, in a suitable solvent, or by exchange reaction with an organic acid salt. The salt formed precipitates after optional concentration of the solution, it is separated by filtration, decantation or freeze-drying. By way of

examples of pharmaceutically acceptable salts, there may be mentioned salts of alkali metals (sodium, potassium, lithium) or of alkaline-earth metals (magnesium, calcium), ammonium salts and azotized base salts (ethanolamine, diethanolamine, triethylamine, trimethylamine, methylamine, propylamine, diisopropylamine, NN-dimethylethanolamine, benzylamine, dicyclohexylamine, N-benzyl-ß-phenethylamine, NN'-dibenzyl-ethylenediamine, diphenylenediamine, benzhydrylamine, quinine, choline, arginine, lysine, leucine, dibenzylamine). When the product of general formula I bears amino or alkylamino radicals, the latter may be converted to addition salts with the acids. By way of examples of addition salts of the pharmaceutically acceptable acids, there may be mentioned salts formed with inorganic acids (hydrochlorides, hydrobromides, nitrates, sulphates, phosphates) or with organic acids (succinates, fumarates, tartrates, acetates, propionates, maleates, citrates, methanesulphonates, paratoluenesulphonates, isothionates or with substitution derivatives of these compounds).

When Q represents a 5-tetrazolyl radical, the products according to the present invention may be converted to metal salts with strong bases. These salts may be obtained by the action of a strong metal base on a product according to the invention in a suitable solvent. By way of examples of pharmaceutically acceptable salts, there may be mentioned the salts of alkali metals (sodium, potassium, lithium).

The following examples are given without implying any limitation and are representative to illustrate the present invention.

In the following examples, chromatographies under pressure are carried out under a pressure of about 50 kPa; solvent evaporations are carried out under a pressure of about 3.3 kPa.

Example 1

4,6-diphenyl-2-pyridone

To a solution of benzylideneacetophenone (41.6 g) and N-carbamoylmethylpyridinium chloride (34.4 g) (prepared according to the method of O. ALBRECHT et al., Helv. Chim. Acta 24, 241E (1941)) in methanol

(600 cc), is added, at room temperature, a 1N aqueous solution of sodium hydroxide (200 cc). The initially yellow solution takes on an orange colour and a yellow solid precipitates. The mixture is stirred at room temperature for 15 minutes and acetic acid (400 cc) is then added. The green solution obtained is stirred for 1 hour at room temperature. The solvent is then distilled in 4 hours under atmospheric pressure. The solid residue obtained is taken up in distilled water (500 cc). After stirring for 1 hour at room temperature, the solid is separated by filtration, washed with distilled water (3 x 100 cc) and dried under reduced pressure at 60°C.(whitish solid; m.p.=209-212°C.)

Example 2

4-(4-chlorophenyl)-6-phenyl-2-pyridone

The procedure in Example 1 is followed but using 3-(4-chlorophenyl)-1-phenyl-2-propen-1-one (10 g), N-carbamoylmethylpyridinium chloride (7.1 g), methanol (150 cc), a 1N aqueous solution of sodium hydroxide (40 cc) and acetic acid (80 cc). The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: methylene chloride-methanol: 95-5). (yellowish solid; m.p.=241-243°C.)

When the procedure of Example 2 is followed and 3-(4-chlorophenyl)-1-phenyl-2-propen-1-one is replaced by the compounds of Table I below then the corresponding products of Table II below are prepared.

Table I

3-(4-methoxyphenyl)-1-phenyl-2-propen-1-one
1-(4-methoxyphenyl)-3-phenyl-2-propen-1-one
1-(4-trifluoromethylphenyl)-3-phenyl-2-propen-1-one
1,3-di(4-chlorophenyl)-2-propen-1-one
1-(4-methylphenyl)-3-phenyl-2-propen-1-one
1-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-propen-1-one
3-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-propen-1-one
3-(2-fluorophenyl)-1-phenyl-2-propen-1-one
1-phenyl-3-(4-trifluoromethylphenyl)-2-propen-1-one
3-(3-methoxyphenyl)-1-phenyl-2-propen-1-one
1,3-di(4-methoxyphenyl)-2-propen-1-one
3-(4-fluorophenyl)-1-phenyl-2-propen-1-one

1-(4-fluorophenyl)-3-phenyl-2-propen-1-one
1-(2-fluorophenyl)-3-phenyl-2-propen-1-one
1-(3-methoxyphenyl)-3-phenyl-2-propen-1-one
3-(3,4-dichlorophenyl)-1-phenyl-2-propen-1-one
3-(4-methylphenyl)-1-phenyl-2-propen-1-one
3-(3-chlorophenyl)-1-phenyl-2-propen-1-one
1-(2-chlorophenyl)-3-phenyl-2-propen-1-one
3-(2-chlorophenyl)-1-phenyl-2-propen-1-one
1-(3-fluorophenyl)-3-phenyl-2-propen-1-one
4-(3-Fluorophenyl)-6-phenyl-2-pyridone
3-(4-fluorophenyl)-1-(2-fluorophenyl)-2-propen-1-one
3-(4-methylthiophenyl)-1-phenyl-2-propen-1-one
3-(3,4-methylenedioxyphenyl)-1-phenyl-2-propen-1-one
3-(3-methylphenyl)-1-phenyl-2-propen-1-one
3-(4-dimethylaminophenyl)-1-phenyl-2-propen-1-one
3-(4-nitrophenyl)-1-phenyl-2-propen-1-one
3-(3-nitrophenyl)-1-phenyl-2-propen-1-one
3-phenyl-1-(2-thienyl)-2-propen-1-one
3-phenyl-1-(3-thienyl)-2-propen-1-one
1-(2-chlorophenyl)-3-(3,4-methylenedioxyphenyl)-2-propen-1-one
3-(4-chlorophenyl)-propenal
2,2-dimethyl-5-phenyl-4-penten-3-one
4-phenyl-3-buten-2-one
1-cyclo-propyl-3-phenyl-2-propen-1-one
1-phenyl-3-(3,4-dimethoxyphenyl)-2-propen-1-one
1-phenyl-3-(4-cyanophenyl)-2-propen-1-one
1-phenyl-3-(3,5-dimethoxyphenyl)-2-propen-1-one

Table II

4-(4-methoxyphenyl)-6-phenyl-2-pyridone (yellowish solid; m.p.=227-229°C.)
6-(4-methoxyphenyl)-4-phenyl-2-pyridone (whitish solid; m.p.=243-245°C.)
6-(4-trifluoromethylphenyl)-4-phenyl-2-pyridone (whitish solid)
4,6-di(4-chlorophenyl)-2-pyridone white solid; (m.p.=297-298°C.)
6-(4-methylphenyl)-4-phenyl-2-pyridone (whitish solid)
6-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-pyridone (m.p.=264°C.)
4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-pyridone (m.p.=270°C.)

4-(2-fluorophenyl)-6-phenyl-2-pyridone (m.p.=211-213°C.)
6-phenyl-4-(4-trifluoromethylphenyl)-2-pyridone (m.p.=228-229°C.)
4-(3-methoxyphenyl)-6-phenyl-2-pyridone (m.p.=187-188°C.)
4,6-di-(4-methoxyphenyl)-2-pyridone (m.p.=260-262°C.)
4-(4-fluorophenyl)-6-phenyl-2-pyridone (m.p.=215°C.)
6-(4-fluorophenyl)-4-phenyl-2-pyridone (m.p.=220°C.)
6-(2-fluorophenyl)-4-phenyl-2-pyridone (m.p.=224-225°C.)
6-(3-methoxyphenyl)-4-phenyl-2-pyridone (m.p.=202-203°C.)
4-(3,4-dichlorophenyl)-6-phenyl-2-pyridone (m.p.=247°C.)
4-(4-methylphenyl)-6-phenyl-2-pyridone (m.p.=248°C.)
4-(3-chlorophenyl)-6-phenyl-2-pyridone (m.p.=209-210°C.)
6-(2-chlorophenyl)-4-phenyl-2-pyridone (m.p.=213°C.)
4-(2-chlorophenyl)-6-phenyl-2-pyridone (m.p.=238°C.)
6-(3-fluorophenyl)-4-phenyl-2-pyridone (m.p.=248°C.)
4-(3-fluorophenyl)-6-phenyl-2-pyridone (m.p.=201°C.)
4-(4-fluorophenyl)-6-(2-fluorophenyl)-2-pyridone (m.p.=225-226°C.)
4-(4-methylthiophenyl)-6-phenyl-2-pyridone (m.p.=228°C.)
4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridone (m.p.=254-255°C.)
4-(3-methylphenyl)-6-phenyl-2-pyridone (m.p.=211°C.)
4-(4-dimethylaminophenyl)-6-phenyl-2-pyridone (m.p.=254-256°C.)
4-(4-nitrophenyl)-6-phenyl-2-pyridone (m.p.=284-285°C.)
4-(3-nitrophenyl)-6-phenyl-2-pyridone (m.p.=210°C.)
4-phenyl-6-(2-thienyl)-2-pyridone (m.p.=212-215°C.)
4-phenyl-6-(3-thienyl)-2-pyridone (m.p.=192-195°C.)
6-(2-chlorophenyl)-4-(3,4-methylenedioxyphenyl)-2-pyridone (m.p.>260°C.)
4-(4-chlorophenyl)-2-pyridone (whitish solid)
6-ter-butyl-4-phenyl-2-pyridone (m.p.=215-217°C.)
6-methyl-4-phenyl-2-pyridone (m.p.= 199-201°C.)
6-cyclo-propyl-4-phenyl-2-pyridone (m.p.= 207-209°C.)
6-phenyl-4-(3,4-dimethoxyphenyl)-2-pyridone (m.p.=233°C.)
6-phenyl-4-(4-cyanophenyl)-2-pyridone (m.p.=262°C.)
6-phenyl-4-(3,5-dimethoxyphenyl)-2-pyridone (m.p.=256°C.)

Example 3

4-phenyl-2-quinolinone

Benzoylacetanilide (150 g) (prepared according to the method of Brown et al., J. Am. Chem. Soc., 79, 2919, (1957)) in concentrated sulphuric acid (76%) (130 cc) is heated for 4 hours at 100°C. The reaction mixture is slowly poured with stirring in distilled water (3150 cc). The precipitate obtained is filtered, washed with water and then with acetone, and dried at 40°C under reduced pressure. The residue obtained is recrystallised in ethanol. (white solid; m.p.=268-269°C.)

When the procedure of Example 3 is followed and benzoyl-acetanilide is replaced by the compounds of Table III below then the corresponding products of Table IV below are prepared.

Table III

(4-chlorobenzoyl)acetanilide
(3-chlorobenzoyl)acetanilide
(2-fluorobenzoyl)acetanilide
(4-fluorobenzoyl)acetanilide
(3,4-dichlorobenzoyl)acetanilide
(4-chlorobenzoyl)acetanilide
(3-chlorobenzoyl)acetanilide
(4-nitrobenzoyl)acetanilide
(3-methoxybenzoyl)acetanilide
(4-methoxybenzoyl)acetanilide
(4-methylthiobenzoyl)acetanilide
(3-toluoyl)acetanilide
(4-toluoyl)acetanilide
(3-methylbenzoyl)acetanilide
(4-trifluoromethylbenzoyl)acetanilide
(4-dimethylaminobenzoyl)acetanilide
2-methyl-3-oxo-3-phenyl-propanilide
benzoyl-p-acetoluidide
(2-methoxybenzoyl)acetanilide
benzoyl-4'-methoxy-acetanilide

Table IV

4-(4-chlorophenyl)-2-quinolinone (m.p.=247-250°C.)
4-(3-chlorophenyl)-2-quinolinone (m.p.=233°C.)
4-(2-fluorophenyl)-2-quinolinone (m.p.=258°C.)
4-(4-fluorophenyl)-2-quinolinone (m.p.=253-254°C.)
4-(3,4-dichlorophenyl)-2-quinolinone (m.p.=255°C.)
6-chloro-4-phenyl-2-quinolinone (m.p.=258°C.)
7-chloro-4-phenyl-2-quinolinone (m.p.=269°C.)
4-(4-nitrophenyl)-2-quinolinone (m.p.=302-303°C.)
4-(3-methoxyphenyl)-2-quinolinone (white solid)
4-(4-methoxyphenyl)-2-quinolinone (white solid)
4-(4-methylthiophenyl)-2-quinolinone (m.p.=226°C.)
4-(3-tolyl)-2-quinolinone (m.p.=209-210°C.)
4-(4-tolyl)-2-quinolinone (m.p.=238-240°C.)
7-methyl-4-phenyl-2-quinolinone (m.p.=267°C.)
4-(4-trifluoromethylphenyl)-2-quinolinone (m.p.>350°C.)
4-(4-dimethylaminophenyl)-2-quinolinone (m.p.=290-293°C.)
4-phenyl-3-methyl-2-quinolinone (m.p.=240-241°C.)
4-phenyl-6-methyl-2-quinolinone (m.p.= 247°C.)
4-(2-methoxyphenyl)-2-quinolinone (m.p.= 241°C.)
6-methoxy-4-phenyl-2-quinolinone (m.p.=253°C.)

Example 4

ethyl 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate

A suspension obtained by mixing 4,6-diphenyl-2-pyridone (2.5 g), ethyl 6-bromohexanoate (3.4 g) and silver carbonate (1.4 g) in toluene (100 cc) is refluxed, protected from light, for 24 hours. After filtration of the reaction mixture, the filtrate is concentrated to dryness at 40°C under reduced pressure. The oily residue obtained is purified by chromatography under pressure, on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 92-8) (yellowish oil).

When the procedure of Example 4 is followed and 6-bromohexanoate is replaced by the compounds of Table V below, then the corresponding product is prepared.

Table V

methyl 6-bromo-2,2-dimethylhexanoate
ethyl 7-bromoheptanoate
ethyl 4-bromobutanoate
ethyl 6-bromohexanoate
ethyl 6-bromohexanoate
ethyl 6-bromo-2-methylhexanoate
methyl 6-bromo-2,2-dimethylhexanoate
ethyl 6-bromo-2-ethyl-2-methylhexanoate
ethyl 7-bromoheptanoate
methyl 6-bromo-2-ethylhexanoate
ethyl 8-bromooctanoate

When the procedure of Example 4 is followed and 4,6-diphenyl-2-pyridone is replaced by the compounds of Table VI below, then the corresponding product is prepared.

Table VI

4-(4-chlorophenyl)-6-phenyl-2-pyridone
6-(4-chlorophenyl)-4-phenyl-2-pyridone
4-(4-methoxyphenyl)-6-phenyl-2-pyridone
6-(4-methoxyphenyl)-4-phenyl-2-pyridone (m.p.=243-245°C)
6-(4-trifluoromethylphenyl)-4-phenyl-2-pyridone
4,6-di(4-chlorophenyl)-2-pyridone
6-(4-methylphenyl)-4-phenyl-2-pyridone
6-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-pyridone
4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-pyridone
6-phenyl-4-(4-trifluoromethylphenyl)-2-pyridone
6-phenyl-4-(3,4-methylenedioxyphenyl)-2-pyridone
4-(3-methoxyphenyl)-6-phenyl-2-pyridone
4,6-di(4-methoxyphenyl)-2-pyridone
4-(4-fluorophenyl)-6-phenyl-2-pyridone
6-(4-fluorophenyl)-4-phenyl-2-pyridone
6-(2-fluorophenyl)-4-phenyl-2-pyridone
6-(3-methoxyphenyl)-4-phenyl-2-pyridone

4-(4-methylphenyl)-6-phenyl-2-pyridone
4-(3-chlorophenyl)-6-phenyl-2-pyridone
6-(2-chlorophenyl)-4-phenyl-2-pyridone
4-(3-chlorophenyl)-6-phenyl-2-pyridone
4-(4-chlorophenyl)-6-phenyl-2-pyridone
4-phenyl-2-quinolinone
4-(4-chlorophenyl)-2-quinolinone
4-(3-chlorophenyl)-2-quinolinone
4-(2-fluorophenyl)-2-quinolinone
4-(4-fluorophenyl)-2-quinolinone
4-(3,4-dichlorophenyl)-2-quinolinone
6-chloro-4-phenyl-2-quinolinone
7-chloro-4-phenyl-2-quinolinone
(4-nitrophenyl)-2-quinolinone
4-(3-methoxyphenyl)-2-quinolinone
4-(4-methoxyphenyl)-2-quinolinone
4-(4-tolyl)-2-quinolinone
4-(3-tolyl)-2-quinolinone
7-methyl-4-phenyl-2-quinolinone
4-(4-trifluoromethylphenyl)-2-quinolinone
4-(4-dimethylaminophenyl)-2-quinolinone
methyl 4-(2-thienyl)-2-quinolinone
4-phenyl-2-pyridone
5,6-diphenyl-2-pyridone
5,6-bis-(4-methoxyphenyl)-2-pyridone
6-phenyl-2-pyridone
4,5-bis-(4-chlorophenyl)-2-pyrimidone
4,5-diphenyl-2-pyrimidone
7-methoxy-3-phenyl-2-quinolinone
4,5-bis-(4-methoxyphenyl)-2-pyrimidone

When the procedure of Example 4 is followed and 4,6-diphenyl-2-pyridone and 6-bromohexanoate are replaced by the compounds of Tables V and VI above, then the corresponding product is prepared. A representative list of compounds so prepared are shown in Table VII below.

Table VII

methyl 2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (brown oil)
ethyl 5-[(4,6-diphenyl-2-pyridyl)oxy]pentanoate (yellowish oil)
ethyl 4-[(4,6-diphenyl-2-pyridyl)oxy]butanoate (yellowish oil).
methyl 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (m.p.=57-58°C.)
ethyl 6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil)
ethyl 6-{[6-(4-chlorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate (m.p.=84-85°C.)
ethyl 6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate
(yellowish solid)
ethyl 6-{[6-(4-methylphenyl)-4-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil).
ethyl 6-{[6-(4-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate.(yellow oil)
ethyl 6-[(4-phenyl-2-quinolyl)oxy]hexanoate
ethyl 2-methyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoate
methyl 2,2-dimethyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoate
ethyl 2-ethyl-2-methyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoate
ethyl 7-[(4-phenyl-2-quinolyl)oxy]heptanoate
6-[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoate
ethyl 2-methyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoate
ethyl 2-ethyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(3-chlorophenyl)-2-quinolyl]oxy}hexanoate
ethyl 2,2-dimethyl-6-{[4-(2-fluorophenyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(4-fluorophenyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(3,4-dichlorophenyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-[(6-chloro-4-phenyl-2-quinolyl)oxy}hexanoate
methyl 2,2-dimethyl-6-[(7-chloro-4-phenyl-2-quinolyl)oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(4-nitrophenyl)-2-quinolyl]oxy}hexanoate
(m.p.=111-112°C.)
methyl 2,2-dimethyl-6-{[4-(3-methoxyphenyl)-2-quinolyl)oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(4-methoxyphenyl)-2-quinolyl]oxy}hexanoate
(m.p.=66-67.5°C.)
ethyl 2-methyl-6-{[4-(4-methoxyphenyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(4-tolyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-[(7-methyl-4-phenyl-2-quinolyl)oxy]hexanoate
methyl 2,2-dimethyl-6-{[4-(4-trifluoromethylphenyl)-2-quinolyl]oxy}hexanoate
methyl 2,2-dimethyl-6-{[4-(2-thienyl)-2-quinolyl]oxy}hexanoate

methyl 2,2-dimethyl-6-[[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (brown-yellowish oil)

methyl 2,2-dimethyl-6-[[4-(4-aminophenyl)-2-quinolyl]oxy}hexanoate (yellow oil)

ethyl 6-[(4-phenyl-2-pyridyl)oxy]hexanoate (oil)

ethyl 6-[(4,6-diphenyl-2-pyrimidyl)oxy]hexanoate (yellow solid)

ethyl 6-[(5,6-diphenyl-2-pyridyl)oxy]hexanoate

methyl 6-[(5,6-diphenyl-2-pyridyl)oxy]-2,2-dimethylhexanoate (m.p.= 85-87°C.)

ethyl 8-[(5,6-diphenyl-2-pyridyl)oxy]octanoate (oil)

ethyl 6-[[5,6-bis-(4-methoxyphenyl)-2-pyridyl]oxy}hexanoate (oil)

ethyl 8-[[5,6-bis-(4-methoxyphenyl)-2-pyridyl]oxy}octanoate (oil)

ethyl 6-[(6-phenyl-2-pyridyl)oxy]hexanoate (oil)

ethyl 7-[(6-phenyl-2-pyridyl)oxy]hexanoate (oil)

methyl 6-[(6-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoate (oil)

ethyl 8-[(6-phenyl-2-pyridyl)oxy]octanoate (oil)

ethyl 6-[4,5-bis-(4-chlorophenyl)-2-pyrimidyloxy]hexanoate (oil)

ethyl 8-(4,5-diphenyl)-2-pyrimidyloxy]octanoate (yellow oil)

ethyl 6-[4,5-bis-(4-methoxyphenyl)-2-pyrimidyloxy]hexanoate (oil)

ethyl 7-[(4,6-diphenyl-2-pyridyl)oxy]heptanoate (yellowish oil)

ethyl 7-(4,5-diphenyl-2-pyrimidyloxy)heptanoate (oil)

methyl 6-(4,5-diphenyl-2-pyrimidyloxy)hexanoate (yellow solid)

ethyl 8-(7-methoxy-3-phenyl-2-quinolyloxy)octanoate (colorless oil)

Example 5

<u>methyl 2,2-dimethyl-7-[(4,6-diphenyl-2-pyridyl)oxy]heptanoate</u>

The suspension obtained by mixing 4,6-diphenyl-2-pyridone (4 g), methyl 7-bromo-2- dimethylheptanoate (8.1 g) (prepared according to the method described in Patent US 4 714 762) and silver carbonate (2.2 g) in dimethylformamide (150 cc) is heated at 100°C., protected from light, for 4 days. The reaction mixture is concentrated to dryness at 40°C under reduced pressure. Excess methyl 7-bromo-2,2-di-methylheptanoate is distilled under reduced pressure (bulb distiller; 100°C. 0.1 mbar). The oily residue obtained is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9-1).(yellowish oil.)

When the procedure of Example 5 is followed and methyl 7-bromo-2,2-dimethylheptanoate is replaced by the compounds of Table VIII below, then the corresponding product is obtained.

Table VIII

ethyl 6-bromo-2-methylhexanoate
methyl 6-bromo-2-ethylhexanoate
ethyl 6-bromo-2-ethyl-2-methylhexanoate
methyl 8-bromo-2,2-dimethyloctanoate
methyl 8-bromo-2,2-dimethyloctanoate
methyl 6-bromo-2,2-dimethylhexanoate
ethyl 6-bromohexanoate
methyl 6-bromo-2,2-dimethylhexanoate
ethyl 6-bromo-2-methylhexanoate
ethyl 8-bromooctanoate
ethyl 6-bromo-2-methylhexanoate
methyl 6-bromo-2,2-dimethylhexanoate
6-bromohexanoate
ethyl 6-bromo-2-methylhexanoate
methyl 3-bromomethylbenzoate
methyl 4-bromomethylbenzoate
methyl 6-bromo-2,2-dimethylhexanoate

When the procedure of Example 5 is followed and 4,6-diphenyl-2-pyridone is replaced by the compounds of Table IX, below then the corresponding product is obtained.

Table IX

6-(4-trifluoromethylphenyl)-4-phenyl-2-pyridone
4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-pyridone
4-(2-fluorophenyl)-6-phenyl-2-pyridone
6-phenyl-4-(4-trifluoromethylphenyl)-2-pyridone
4-(3-methoxyphenyl)-6-phenyl-2-pyridone
4,6-di(4-methoxyphenyl)-2-pyridone
4-(4-fluorophenyl)-6-phenyl-2-pyridone

6-(2-fluorophenyl)-4-phenyl-2-pyridone
6-(3-methoxyphenyl)-4-phenyl-2-pyridone
4-(3,4-dichlorophenyl)-6-phenyl-2-pyridone
4-(4-methylphenyl)-6-phenyl-2-pyridone
4-(3-chlorophenyl)-6-phenyl-2-pyridone
6-(2-chlorophenyl)-4-phenyl-2-pyridone
4-(2-chlorophenyl)-6-phenyl-2-pyridone
4-(3-chlorophenyl)-6-phenyl-2-pyridone
4-(4-chlorophenyl)-6-phenyl-2-pyridone
6-(4-chlorophenyl)-4-phenyl-2-pyridone
4-(3-chlorophenyl)-6-phenyl-2-pyridone
6-(2-fluorophenyl)-4-phenyl-2-pyridone
6-(3-fluorophenyl)-4-phenyl-2-pyridone
4-(3-fluorophenyl)-6-phenyl-2-pyridone
4-(4-fluorophenyl)-6-phenyl-2-pyridone
4-(4-fluorophenyl)-6-(2-fluorophenyl)-2-pyridone
4-(3-methoxyphenyl)-6-phenyl-2-pyridone
4-(4-methylthiophenyl)-6-phenyl-2-pyridone
4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridone
4-(3-methylphenyl)-6-phenyl-2-pyridone
4-(4-methylphenyl)-6-phenyl-2-pyridone
4-(4-dimethylaminophenyl)-6-phenyl-2-pyridone
4-(4-nitrophenyl)-6-phenyl-2-pyridone
4-phenyl-6-(2-thienyl)-2-pyridone
4-phenyl-6-(3-thienyl)-2-pyridone
4-(3-tolyl)-2-quinolinone
4-(4-nitrophenyl)-6-phenyl-2-pyridone
4-(3-nitrophenyl)-6-phenyl-2-pyridone
6-(2-chlorophenyl)-4-(3,4-methylenedioxyphenyl)-2-pyridone,
4-phenyl-3-methyl-2-quinolinone
4-(4-chlorophenyl)-2-pyridone
6-ter-butyl-4-phenyl-2-pyridone
6-methyl-4-phenyl-2-pyridone
6-cyclo-propyl-4-phenyl-2-pyridone
6-cyclo-propyl-4-phenyl-2-pyridone
6-methyl-4-phenyl-2-quinolinone
4-(2-methoxyphenyl)-2-quinolinone

6-methoxy-4-phenyl-2-quinolinone
6-phenyl-4-(3,4-dimethoxyphenyl)-2-pyridone

When the procedure of Example 5 is followed and 4,6-diphenyl-2-pyridone is replaced by a compound selected from Table VI or Table IX and methyl 7-bromo-2,2-dimethylheptanoate is replaced by a compound selected from Table V or Table VIII, then the corresponding product is obtained. Representative compounds so prepared are identified in Table X below.

Table X

ethyl 2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (reddish oil)
methyl 2-ethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (yellow oil)
ethyl 2-ethyl-2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (yellow oil)
methyl 2,2-dimethyl-8-[(4,6-diphenyl-2-pyridyl)oxy]octanoate (yellow oil)
methyl 2,2-dimethyl-6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil).
methyl 2,2-dimethyl-6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (colorless oil).
ethyl 2-methyl-6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (colorless oil).
ethyl 6-{[4-(2-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)
ethyl 6-{[6-phenyl-4-(4-trifluoromethylphenyl)-2-yridyl]oxy}hexanoate. (yellowish oil)
ethyl 6-{[4-(3-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (colorless oil).
methyl 2,2-dimethyl-6-{[4-(3-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)
ethyl 6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)
methyl,2,2-dimethyl-6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil)
ethyl 6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate (colorless oil).
ethyl 6-{[4-(4-methylphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil).
ethyl 6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil).
ethyl 6-{[6-(2-chlorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil).
ethyl 6-{[4-(2-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (orange oil).
ethyl 2-methyl-6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)

ethyl 2-methyl-6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil).

methyl 6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (m.p.=97-98°C.)

ethyl 2-methyl-6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)

methyl 2,2-dimethyl-6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)

ethyl 6-{[6-(3-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate (colorless oil)

ethyl 6-{[4-(3-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)

ethyl 2-methyl-6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil).

ethyl 6-{[4-(4-fluorophenyl)-6-(2-fluorophenyl)-2-pyridyl]oxy}hexanoate (yellow oil)

ethyl 2-methyl-6-{[4-(3-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)

ethyl 6-{[4-(4-methylthiophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (m.p.=55°C.)

ethyl 6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (white solid)

ethyl 2-methyl-6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy} hexanoate (yellowish oil)

ethyl 6-{[4-(3-methylphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate.(yellowish oil)

ethyl 2-methyl-6-{[4-(4-methylphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellowish oil)

ethyl 6-{[4-(4-dimethylaminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate. (yellow solid)

ethyl 6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (m.p.=75-76°C.)

ethyl 6-{[4-phenyl-6-(2-thienyl)-2-pyridyl]oxy}hexanoate (yellow oil).

methyl 2,2-dimethyl-6-{[4-phenyl-6-(2-thienyl)-2-pyridyl]oxy}hexanoate (yellowish oil)

ethyl 6-{[4-phenyl-6-(3-thienyl)-2-pyridyl]oxy}hexanoate.(yellow oil)

methyl 2,2-dimethyl-6-{[4-phenyl-6-(3-thienyl)-2-pyridyl]oxy}hexanoate (yellowish oil)

ethyl 8-[(4-phenyl-2-quinolyl)oxy]octanoate.

methyl 2,2-dimethyl-6-{[4-(3-tolyl)-2-quinolyl]oxy}hexanoate.

methyl 2,2-dimethyl-6-{[4-(4-dimethylaminophenyl)-2-quinolyl]oxy}hexanoate

ethyl 6-[[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate
ethyl 6-[[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate
ethyl 2-methyl-6-[[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)
ethyl 2-methyl-6-[[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)
methyl 2,2-dimethyl-6-[[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy} hexanoate.(m.p.=90-91°C.)
methyl 2,2-dimethyl-6-[[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (m.p.=90-91°C.)
ethyl 6-[[4-(3-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (yellow oil)
ethyl 6-[[6-(2-chlorophenyl)-4-(3,4-methylenedioxyphenyl)-2-pyridyl]oxy}-2-methylhexanoate (oil).
ethyl 6-[[6-(2-chlorophenyl)-4-phenyl-2-pyridyl]oxy}-2-methylhexanoate (oil)
methyl 2,2-dimethyl-6-[(3-methyl-4-phenyl-2-quinolyl)oxy]hexanoate (oil)
methyl 6-[(4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoate (oil)
methyl 6-[[4-(4-chlorophenyl)-2-pyridyl]oxy}-2,2-dimethylhexanoate (oil)
ethyl 6-[(6-ter-butyl-4-phenyl-2-pyridyl)oxy]hexanoate (oil)
methyl 6-[(6-ter-butyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoate (oil)
ethyl 6-[(6-methyl-4-phenyl-2-pyridyl)oxy]hexanoate (oil)
methyl 6-[(6-methyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoate (oil)
ethyl 6-[(6-cyclo-propyl-4-phenyl-2-pyridyl)oxy]hexanoate (oil)
methyl 6-[(6-cyclo-propyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoate (oil)
methyl 6-[(6-methyl-4-phenyl-2-quinolyl)oxy]-2,2-dimethylhexanoate (oil)
methyl 6-[4-(2-methoxyphenyl)-2-quinolyl]oxy}-2,2-dimethylhexanoate (oil)
ethyl 6-[(6-methoxy-4-phenyl-2-quinolyl)oxy]hexanoate (oil)
ethyl 6-[[6-phenyl-4-(3,4-dimethoxyphenyl)-2-pyridyl]oxy}hexanoate (oil)
4-[(4,6-diphenyl-2-pyridyl)oxymethyl]benzoate (m.p.= 115°C.)
methyl 3-[(4,6-diphenyl-2-pyridyl)oxymethyl]benzoate (oil)
methyl 6-[(4,6-diphenyl-2-pyrimidyl)oxy]-2,2-dimethylhexanoate (yellow solid)

Example 6

6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid

To a solution of ethyl 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (3.7 g) in ethanol (100 cc) are added sodium hydroxide pellets (0.6 g). The reaction mixture is refluxed for 1 hour and then concentrated to dryness under

reduced pressure. The residue obtained is dissolved in distilled water (150 cc). The pH of the aqueous phase is brought to about 5 by addition of a 2N aqueous solution of hydrochloric acid. It is then extracted with methylene chloride (3 × 50 cc). The organic phases are combined, washed with distilled water (3 × 50 cc), dried over sodium sulphate and concentrated to dryness at 40°C under reduced pressure. The solid residue obtained is purified by recrystallization in an n-hexane-ethyl acetate (10-1) mixture (55 cc). (white crystals; m.p.=87-88°C.)

When the procedure of Example 6 is followed and 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate is replaced by a compound selected from, Table VII or Table X, then the corresponding product is prepared. Representative compounds so prepared are identified in Table XI below.

Table XI

2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid (m.p.=109-111°C.)

7-[(4,6-diphenyl-2-pyridyl)oxy]heptanoic acid (white crystals; m.p.=104-106°C.)

5-[(4,6-diphenyl-2-pyridyl)oxy]pentanoic acid (m.p.=160-163°C.)

4-[(4,6-diphenyl-2-pyridyl)oxy]butanoic acid (m.p.=125-128°C.)

2,2-dimethyl-7-[(4,6-diphenyl-2-pyridyl)oxy]heptanoic acid (m.p.=98-99°C.)

2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid (m.p.=87-88°C.)

2-ethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid (m.p.=115°C.)

2-ethyl-2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid (m.p.=119-120°C.)

2,2-dimethyl-8-[(4,6-diphenyl-2-pyridyl)oxy]octanoic acid (m.p.=80°C.)

6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=108-110°C.)

2,2-dimethyl-6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=101-103°C.)

6-{[6-(4-chlorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=103-105°C.)

6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=74-76°C.)

2,2-dimethyl-6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=108.5°C.)

2-methyl-6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=86°C.)

6-{[6-(4-methoxyphenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=88-90°C.)

6-{[6-(4-trifluoromethylphenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid

(m.p.=113-114°C.)
6-{[4,6-di(4-chlorophenyl)-2-pyridyl]oxy}hexanoic acid (m.p.=84-86°C)
6-{[6-(4-methylphenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=76-78°C.).
6-{[6-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-pyridyl]oxy}hexanoic acid
(m.p.=110-112°C.)
6-{[4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-pyridyl]oxy}hexanoic acid
(m.p.=129-130°C.)
6-{[4-(2-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=100-101°C.)
6-{[6-phenyl-4-(4-trifluoromethylphenyl)-2-pyridyl]oxy}hexanoic acid
(m.p.=90-91°C.)
6-{[4-(3-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=115-116°C.)
2,2-dimethyl-6-{[4-(3-Methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=89°C.)
6-{[4,6-di(4-methoxyphenyl)-2-pyridyl]oxy}hexanoic acid (m.p.=118°C.)
6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=95-96°C.)
2,2-dimethyl-6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=119-121°C.)
6-{[6-(4-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=94-95°C.)
6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=86-87°C.)
6-{[6-(3-methoxyphenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=91°C.)
6-{[4-(3,4-dichlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=101°C.)
6-{[4-(4-methylphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=101-
102°C.)
6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=61-63°C.)
sodium 6-{[6-(2-chlorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoate
(m.p.=255°C.dec.).
6-{[4-(2-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=73°C dec.)
2-methyl-6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=55-57°C.)
2-methyl-6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=97-98°C.)
2,2-dimethyl-6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=118°C.)
2-methyl-6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=87°C.)

2,2-dimethyl-6-[[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=133°C.)

6-[[6-(3-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=93°C.)

6-[[4-(3-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=101°C.)

2-methyl-6-[[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=101°C.)

6-[[4-(4-fluorophenyl)-6-(2-fluorophenyl)-2-pyridyl]oxy}hexanoic acid (m.p.=86°C.)

2-methyl-6-[[4-(3-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=103°C.)

6-[[4-(4-methylthiophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=104.5°C.)

6-[[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=124-126°C.)

2-methyl-6-[[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=123-125°C.)

6-[[4-(3-methylphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=67°C.)

2,2-dimethyl-6-[[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy} hexanoic acid (m.p.=166-167°C.)

2-methyl-6-[[4-(4-methylphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=83-85°C.)

6-[[4-(4-dimethylaminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=159°C.)

6-[[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=118-119°C.)

6-[[4-phenyl-6-(2-thienyl)-2-pyridyl]oxy}hexanoic acid (m.p.=71-73°C.)

2,2-dimethyl-6-[[4-phenyl-6-(2-thienyl)-2-pyridyl]oxy}hexanoic acid (m.p.=121-122°C.)

6-[[4-phenyl-6-(3-thienyl)-2-pyridyl]oxy}hexanoic acid (m.p.=109-110°C.)

2,2-dimethyl-6-[[4-phenyl-6-(3-thienyl)-2-pyridyl]oxy}hexanoic acid (m.p.=104-106°C.)

6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid (m.p.=80-81°C.)

2-methyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid (m.p.=81°C.)

2,2-dimethyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid (m.p.=118-120°C.)

2-ethyl-2-methyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid (colorless oil; I.R. (KBr): 1697 cm^{-1}.)

7-[(4-phenyl-2-quinolyl)oxy]heptanoic acid (m.p.=62-65°C.)

8-[(4-phenyl-2-quinolyl)oxy]octanoic acid (.m.p.=68°C)

6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoic acid.(m.p.=75-77°C.)
2-methyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=103-104°C.)
2-ethyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoic acid (m.p.=122-123°C.)
2,2-dimethyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=110-111°C.)
2,2-dimethyl-6-{[4-(3-chlorophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=115°C.)
2,2-dimethyl-6-{[4-(2-fluorophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=91°C.)
2,2-dimethyl-6-{[4-(4-fluorophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=78-79°C.)
2,2-dimethyl-6-{[4-(3,4-dichlorophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=163-164°C.)
2,2-dimethyl-6-[(6-chloro-4-phenyl-2-quinolyl)oxy}hexanoic acid (m.p.=141°C.)
2,2-dimethyl-6-[(7-chloro-4-phenyl-2-quinolyl)oxy}hexanoic acid (m.p.=102°C.)
2,2-dimethyl-6-{[4-(4-nitrophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=85-92°C.)
2,2-dimethyl-6-{[4-(3-methoxyphenyl)-2-quinolyl)oxy}hexanoic acid
[yellowish oil; I.R. (KBr)1699 cm^{-1}]
2,2-dimethyl-6-{[4-(4-methoxyphenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=108-109°C.)
2-methyl-6-{[4-(4-methoxyphenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=80-81°C.)
2,2-dimethyl-6-{[4-(3-tolyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=78-79°C.)
2,2-dimethyl-6-{[4-(4-tolyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=93-94°C.)
2,2-dimethyl-6-[(7-methyl-4-phenyl-2-quinolyl)oxy]hexanoic acid
(colorless oil).
2,2-dimethyl-6-{[4-(4-trifluoromethylphenyl)-2-quinolyl]oxy}hexanoic
acid (m.p.=128-129°C.)
2,2-dimethyl-6-{[4-(4-dimethylaminophenyl)-2-quinolyl]oxy}hexanoic
acid (m.p.=121-122°C.)
2,2-dimethyl-6-{[4-(2-thienyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=132-134°C.)
2-methyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid

(m.p.=134-136°C.)

6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=131-133°C.)

2,2-dimethyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=123-125°C.)

6-{[4-(4-methylaminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=115-117°C.)

6-{[4-(4-isopropylaminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=101°C.)

6-{[4-(4-methylaminophenyl)-6-phenyl-2-pyridyl]oxy}-2,2-dimethylhexanoic acid (m.p.=144°C.)

6-{[6-(2-chlorophenyl)-4-(3,4-methylenedioxyphenyl)-2-pyridyl]oxy}-2-methylhexanoic acid (m.p.=109°C.).

6-{[6-(2-chlorophenyl)-4-phenyl-2-pyridyl]oxy}-2-methylhexanoic acid (m.p.=89°C.)

2,2-dimethyl-6-[(3-methyl-4-phenyl-2-quinolyl)oxy]hexanoic acid (m.p.=148-149°C.)

2,2-dimethyl-6-[(4-phenyl-2-quinolyl)amino]hexanoic acid (m.p.=176-177°C.)

2,2-dimethyl-6-[(4-phenyl-2-quinolyl)thio]hexanoic acid (m.p.=99-100°C.)

6-[(4-phenyl-2-pyridyl)oxy]hexanoic acid (m.p.=54-56°C.)

6-[(4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid (m.p.=121.5°C.)

6-{[4-(4-chlorophenyl)-2-pyridyl]oxy}-2,2-dimethylhexanoic acid (m.p.=88-90°C.)

6-[(6-ter-butyl-4-phenyl-2-pyridyl)oxy]hexanoic acid (m.p.=71-73°C.)

6-[(6-ter-butyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid (m.p.=82-84°C.)

6-[(6-methyl-4-phenyl-2-pyridyl)oxy]hexanoic acid (m.p.=67-69°C.)

6-[(6-methyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid (m.p.=114-116°C.)

6-[(6-cyclopropyl-4-phenyl-2-pyridyl)oxy]hexanoic acid (m.p.=86-88°C.)

6-[(6-cyclopropyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid (m.p.=90°C.)

6-[(6-methyl-4-phenyl-2-quinolyl)oxy]-2,2-dimethylhexanoic acid (m.p.=

6-{[4-(2-methoxyphenyl)-2-quinolyl]oxy}-2,2-dimethylhexanoic acid (m.p.=152°C.)

6-[(6-methoxy-4-phenyl-2-quinolyl)oxy]hexanoic acid
(m.p.=108-110°C.)
6-[[6-phenyl-4-(3,4-dimethoxyphenyl)-2-pyridyl]oxy}hexanoic acid
(m.p.=103°C.)
6-[[6-phenyl-4-(4-carboxyphenyl)-2-pyridyl]oxy}hexanoic acid
(m.p.=166-168°C.)
6-[[6-phenyl-4-(3,5-dimethoxyphenyl)-2-pyridyl]oxy)hexanoic acid
(m.p.=99°C.)
4-[(4,6-diphenyl-2-pyridyl)oxymethyl]benzoic acid (m.p.=203°C.)
3-[(4,6-diphenyl-2-pyridyl)oxymethyl]benzoic acid (m.p.=174°C.)
N-[4-(4,6-diphenyl-2-pyridyloxy)butanoyl]glycine (m.p.=182°C.)
6-[(4,6-diphenyl-2-pyrimidyl)oxy]hexanoic acid (m.p.=104-105°C.)
6-[(4,6-diphenyl-2-pyrimidyl)oxy]-2,2-dimethylhexanoic acid (m.p.=127-129°C.)
6-[(5,6-diphenyl-2-pyridyl)oxy]hexanoic acid (m.p.=141-142°C.)
6-[(5,6-diphenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid (m.p.=116-117°C.)
sodium 8-[(5,6-diphenyl-2-pyridyl)oxy]octanoate (IR : 1562 cm^{-1})
6-[[5,6-bis-(4-methoxyphenyl)-2-pyridyl]oxy}hexanoic acid (m.p.=98°C.)
8-[[5,6-bis-(4-methoxyphenyl)-2-pyridyl]oxy}octanoic acid (m.p.=107°C.)
6-[(6-phenyl-2-pyridyl)oxy]hexanoic acid (m.p.=63°C.)
7-[(6-phenyl-2-pyridyl)oxy]heptanoic acid (m.p.=55°C.)
6-[(6-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid (m.p.=74-75°C.)
sodium 8-[(6-phenyl-2-pyridyl)oxy]octanate (IR: 1563 cm^{-1})
6-[4,5-bis-(4-chlorophenyl)-2-pyrimidyloxy]hexanoic acid (m.p.=153°C.)
2,2-dimethyl-8-(4,5-diphenyl-2-pyrimidylthio)octanoic acid (m.p.=109°C.)
9-(4,5-diphenyl-2-pyrimidylthio)nonanoic acid (m.p.=90-92°C.)
8-(4,5-diphenyl-2-pyrimidyloxy)octanoic acid (m.p.=106°C.)
6-[4,5-bis-(4-methoxyphenyl)-2-pyrimidyloxy]hexanoic acid (m.p.=142-143°C.)
7-(4,5-diphenyl-2-pyrimidyloxy)heptanoic acid (m.p.=178-80°C.)
6-(4,5-diphenyl-2-pyrimidyloxy)hexanoic acid (m.p.= 141-142°C.)
6-(4,5-diphenyl-2-pyrimidylthio)hexanoic acid (m.p.= 103-105°C.)
sodium 8-(4,5-diphenyl-2-pyrimidylthio)octanoate (IR: 1562 cm^{-1})
sodium 8-(7-methoxy-3-phenyl-2-quinolylthio)octanoate (IR: 1562 cm^{-1})
sodium 8-(7-methoxy-3-phenyl-2-quinolyloxy)octanoate (IR:1564 cm^{-1})
sodium 8-(4-phenyl-2-quinazolylthio)octanoate (IR : 1563 cm^{-1})
sodium 8-[(4-phenyl-2-quinolyl)thio]octanoate (IR : 1563 cm^{-1})

Example 7

6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile

The procedure of Example 4 is followed using 4,6-diphenyl-2-pyridone (6.18 g) and 6-bromohexanonitrile (6.60 g) in place of 6-bromo-hexanoate, silver carbonate (6.89 g) and toluene (300 cc) and the reaction mixture is refluxed for 72 hours. The material formed is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9.5-0.5).to obtain 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile as a white solid which is used directly in subsequent reactions.

When the procedure of Example 7 is followed and 4,6-diphenyl-2-pyridone is replaced by a compound selected from Table VI or Table II, then the corresponding compound is prepared.

Similarly, as described in Example 7, when the procedure of Example 4 is followed and 6-bromohexanonitrile or 6-bromo-2,2-dimethylhexanonitrile are used in place of the ethyl ester, and are reacted with compounds selected from Table VI, then the corresponding compound is prepared. Representative compounds so prepared are described below in Table XIA.

Table XIA

2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile.(m.p.=71°C.)

6-[(4-phenyl-2-quinolyl)oxy]hexanonitrile (yellowish oil)

2,2-dimethyl-6-[(4-phenyl-2-quinolyl)oxy]hexanonitrile (m.p.=35°C.)

2,2-dimethyl-6-{[4-(4-chlorophenyl)2-quinolyl]oxy}hexanonitrile (m.p.=29°C.)

6-{[4-(4-chlorophenyl)2-quinolyl]oxy}hexanonitrile (m.p.=32°C.)

6-{[6-phenyl-4-(3,4-methylenedioxyphenyl)2-pyridyl]oxy}hexanonitrile (m.p.=108°C.)

6-{[5-phenyl-4-(3,4-methylenedioxyphenyl)2-pyridyl]oxy}-2,2-dimethyl-hexanonitrile (m.p.=108°C.)

Example 8

6-[(4,6-diphenyl-2-pyridyl)oxy]hexanamide

Dry hydrochloric acid is bubbled for 4 hours in a solution of 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile (2.5 g) in formic acid (98-100%),(1.1 cc). The reaction mixture is then taken up in ethyl acetate (100 cc). The organic

phase is washed with 1N sodium hydroxide, dried over sodium sulphate and concentrated to dryness at 40°C under reduced pressure. The solid residue obtained is purified by recrystallization in toluene.to obtain 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanamide as white crystals. (m.p.=118-120°C.)

When the procedure of Example 8 is followed and 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile is replaced by a compound prepared according to Example 7, such as those identified in Table XIA, then the corresponding product is prepared.

Example 9

5-[[5-(4,6-diphenyl-2-pyridyl)oxy]pentyl]-[1H]-tetrazole

To a solution of 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile (5 g) in dimethylformamide (50 cc), are added sodium nitride (3.8 g) and ammonium chloride (3.1 g). The reaction mixture is heated at 120°C for 96 hours and then taken up in distilled water (100 cc). After extraction with ethyl acetate (100 cc), the organic phase is washed with distilled water (2 x 50 cc), dried over sodium sulphate and concentrated to dryness, at 40°C., under reduced pressure. The residue thus obtained is purified by chromatography under pressure on silica gel (30-60 mm; n-hexane-ethyl acetate 1-1) and then by recrystallization in toluene to obtain 5-[[5-(4,6-diphenyl-2-pyridyl)oxy]pentyl]-[1H]-tetrazole as white crystals. (m.p.=144-145°C.)

When the procedure of Example 9 is followed and 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile is replaced by a compound prepared according to Example 7, then the representative compounds of Table XII below are prepared.

Table XII

5-[1,1-dimethyl-5-[(4,6-diphenyl-2-pyridyl)oxy]pentyl]-[1H]-tetrazole (m.p.=160-162°C.)

5-[5-[(4-phenyl-2-quinolyl)oxy]pentyl]-[1H]-tetrazole (m.p.=134°C.)

5-[1,1-dimethyl-5-[(4-phenyl-2-quinolyl)oxy]pentyl]-[1H]-tetrazole (m.p.=170-172°C.)

5-[1,1-dimethyl-5-[[4-(4-chlorophenyl)-2-quinolyl]oxy}pentyl]-[1H]-tetrazole.(m.p.=165-167°C.)

5-[5-[[4-(4-chlorophenyl)-2-quinolyl]oxy}pentyl]-[1H]-tetrazole (m.p.=92-94°C.)

Example 10

5-{5-[[6-phenyl-4-(3,4-methylenedioxyphenyl)-2-pyridyl]oxy}pentyl }-1H-tetrazole

By using a similar procedure to that described in example 9 but with 2.4 g 6-{[6-phenyl-4-(3,4-methylenedioxyphenyl)-2-pyridyl]oxy}-hexanonitrile, 1.65g of sodium azide, 1.3 g of triethylamine hydrochloride (in place of ammonium chloride) and 90 cc of N-methylpyrrolidone (in place of dimethylformamide) as the starting material (70 hours; 150°C.), and after purification by flash chromatography on silica gel (30-60mm; eluent: ethyl acetate) and recristallization from 18 cc of acetonitrile gives 5-{5-[[6-phenyl-4-(3,4-methylenedioxyphenyl)-2-pyridyl]oxy}pentyl }-1H-tetrazole (m.p.=150°C.)

When the procedure of Example 10 is followed but using 5-{6-[[6-phenyl-4-(3,4-methylenedioxyphenyl)-2-pyridyl]oxy}-2-methyl-2-hexanonitrile then the product prepared is 5-{6-[[6-phenyl-4-(3,4-methylenedioxyphenyl)-2-pyridyl]-oxy}-2-methyl-2-hexyl}-1H-tetrazole. (m.p.=198°C.)

Example 11

3-[(4,6-diphenyl-2-pyridyl)oxy]-1-propanol

The procedure in Example 4 is followed but using 4,6-diphenyl-2-pyridone (15 g), freshly distilled 3-bromo-1-propanol (16.5 cc), silver carbonate (8.4 g) and toluene (600 cc). The reaction mixture is refluxed for 144 hours. The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 7-3). (white solid; m.p.=94°C.)

Example 12

sodium 2-{3-[(4,6-diphenyl-2-pyridyl)oxy]propyloxy}acetate

To potassium tert-butylate (5.52 g) in tert-butanol (60 cc) heated to 100°C is added, in the form of a homogeneous solid, a mixture of 3-[(4,6-diphenyl-2-pyridyl)oxy]-1-propanol (5 g) and potassium 2-bromoacetate (4.35 g). The addition is carried out in 1 hour. The reaction mixture is then heated for 48 hours at 100°C. and then poured in iced water (100 g). The pH of the aqueous phase is brought to 5 by addition of 1N hydrochloric acid. The mixture is then extracted with dichloromethane (3 x50 cc) after saturating the aqueous

phase with sodium chloride. The combined organic phases are dried over sodium sulphate and concentrated to dryness at 40°C. under reduced pressure. The oily residue obtained is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-diethyl ether 65-35 and then 40-60 and then diethyl ether-methanol;9-1). The white solid obtained, taken up in acetone (5 cc), is treated with sodium hydroxide pellets (0.19 g) and distilled water (1.cc). The mixture is stirred for 60 hours at room temperature. The precipitate obtained is filtered, washed with ethyl ether and dried at 40°C.under reduced pressure. (white solid; m.p.=285-288°C.)

Example 13

ethyl 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate

The yellow suspension obtained by mixing ethyl 6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (5.3 g), stannous chloride (11.6 g) in ethanol (100 cc) is heated at 70°C. for 2 hours and 30 minutes under inert atmosphere. The clear brown solution thus obtained is concentrated to dryness under reduced pressure. The residue obtained is taken up in distilled water (100 cc). The pH of this aqueous phase is brought to 6 by addition of sodium hydrogenocarbonate. The solution is then extracted with ethyl acetate (3 x 200 cc). The organic phases are combined, washed with distilled water (3 x 50 cc), dried over sodium sulphate and concentrated to dryness at 40°C. under reduced pressure. The residue obtained is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 7-3). (yellowish oil).

When the procedure of Example 13 is followed and ethyl 6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate is replaced by a compound selected from Table XIII below, then the corresponding compound of Table XIV below is prepared.

Table XIII

ethyl 2-methyl-6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate. (yellow oil)

ethyl 2-methyl-6-{[4-(3-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate.

methyl 2,2-dimethyl-6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoate.(m.p.90-91°C.)

methyl 2,2-dimethyl-6-{[4-(4-nitrophenyl)-2-quinolyl]oxy}hexanoate
methyl 6-{[4-(3-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate
(yellow oil)

Table XIV

ethyl 2-methyl-6-{[4-(4-aminophenyl)6-phenyl-2-pyridyl]oxy}hexanoate
(yellow oil)
ethyl 2-methyl-6-{[4-(3-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate.
methyl 2,2-dimethyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate
(brown-yellowish oil)
methyl 2,2-dimethyl-6-{[4-(4-aminophenyl)-2-quinolyl]oxy}hexanoate
(yellow solid)
methyl 6-{[4-(3-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate
(yellow oil)

Example 14

6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid

The procedure in Example 4 is followed but using ethyl 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoate (3.9 g), potassium hydroxide pellets (0.81 g) dissolved in distilled water (10 cc), and ethanol (150 cc). The reaction mixture is refluxed for 2 hours. The product is purified by recrystallization in toluene (70 cc) to obtain 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid as yellowish crystals; (m.p.=131-133°C.)

When the procedure of Example 14 is followed and 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoate is replaced by a compound selected from Tables XIII or XIV then the corresponding compound of Table XV below is prepared.

Table XV

2-methyl-6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
2-methyl-6-{[4-(3-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
2,2-dimethyl-6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
2,2-dimethyl-6-{[4-(4-nitrophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=150-151°C.)

6-{[4-(3-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
2-methyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
(m.p.=134-136°C.)
2-methyl-6-{[4-(3-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid
2,2-dimethyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid.
(m.p.=123-125°C.)
2,2-dimethyl-6-{[4-(4-aminophenyl)-2-quinolyl]oxy}hexanoic acid
(m.p.=150-151°C.)
6-{[4-(3-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid (m.p.=101°C.)

Example 15

ethyl 2-methyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate

The procedure in Example 12 is followed but using ethyl 2-methyl-6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (2.5 g), stannous chloride (5.3 g) and ethanol (100 cc). The residue, after extraction and concentration of the organic phases to dryness, is used as it is in the next stage.(yellow oil)

Example 16

ethyl 6-{[4-(4-methylaminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate

The mixture comprising (3 g) 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate from Example 13, Table XIII, ethyl ortho-formate (5.5 cc) and trifluoroacetic acid 25 drops is refluxed for 17 hours. The reaction mixture is then concentrated to dryness, at 80°C, under reduced pressure (0.13 kPa). The oily residue obtained (3.5 g) is taken up in ethanol (40 cc). To the yellow suspension thus obtained, cooled to 5°C. on an ice bath, is slowly added sodium borohydride (1.1 g). The reaction mixture is then refluxed for 1 hour. The solution obtained is poured in iced water (100 cc), extracted with ethyl ether (100 cc). The combined organic phases are washed with distilled water until neutrality, dried over sodium sulphate and concentrated to dryness at 40°C under reduced pressure. The oily residue obtained is purified by chromatography under pressure on silica gel (30-60µmm; eluent: n-hexane-ethyl acetate as a yellow oil)

When the procedure of Example 16 is followed and ethyl 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate is replaced with methyl 6-{[4-

(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}-2,2-dimethylhexanoate then the compound prepared is methyl 6-{[4-(4-methylaminophenyl)-6-phenyl-2-pyridyl]oxy}-2,2-dimethylhexanoate. (m.p.=77°C.)

Example 17

ethyl 6-{[4-(4-isopropylaminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate

To a solution of ethyl 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (3 g) and acetone (0.54 cc) in acetic acid (45 cc), brought to 15°C, is slowly added sodium borohydride (1.14 g) so as to maintain the temperature below 22°C. The mixture is then stirred at room temperature for 4 hours. The reaction mixture is then poured in distilled water (150 cc) and extracted with ethyl ether (2 x 100 cc). The combined organic phases are washed with distilled water until neutrality, dried over sodium sulphate and concentrated to dryness at 40°C under reduced pressure. The oily residue obtained is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9-1 as a yellow oil)

Example 18

6-{[4-(4-benzamidophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid

To a solution of ethyl 6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (4 g), triethylamine (1.7 cc) and a spatula-tip-full of 4-dimethylaminopyridine (DMAP) in chloroform (40 cc), is slowly added, at room temperature, benzoyl chloride (1.38 cc) in solution in chloroform (20 cc). The temperature rises up to 33°C. The reaction mixture is then stirred at room temperature for 21 hours and then hydrolysed with distilled water (50 cc). The organic phase is decanted. The aqueous phase is extracted with dichloromethane (2 x 50 cc). The combined organic phases are washed with distilled water until neutrality, dried over sodium sulphate and concentrated to dryness at 40°C under reduced pressure. The product is used directly in the next reaction after purification by recrystallization in an n-hexane-ethyl acetate (1-1) mixture (100 cc). The procedure in Example 3 is then followed but using the ethyl 6-{[4-(4-benzamidophenyl)-6-phenyl-2-pyridyl]oxy}hexanoate previously obtained, potassium hydroxide pellets (0.7 g) dissolved in distilled water (15 cc) and ethanol (150 cc). The reaction mixture is refluxed for 2 hours.

The product is purified by recrystallization in ethyl acetate (50 cc), whitish crystals (m.p.=167-169°C.)

Example 19

6-[[4-(4-trifluoroacetamidophenyl)-6-phenyl-2-pyridyl]oxy]hexanoic acid

To a solution of 6-[[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy]-hexanoic acid (1 g) in tetra-hydrofuran (15 cc) is slowly added, at 0°C, trifluoroacetic anhydride (0.5 cc). The reaction mixture is stirred for 1 hour at room temperature and then poured on ice. The tetrahydrofuran is then evaporated at 25°C under reduced pressure, the remaining aqueous phase is then extracted with chloroform. The organic phase is washed with distilled water until neutrality and dried over sodium sulphate and then concentrated to dryness at 40°C under reduced pressure. The solid residue obtained is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 4-6) and then by two successive recrystallizations, the first in an n-hexane-ethyl acetate (3-5) mixture (40 cc), the second in toluene (20 cc), yellowish crystals; (m.p.=178-180°C.)

Example 20

8-[(4-phenyl-2-quinolyl)oxy]octanoic acid

To a suspension of potassium tert-butylate (26 g) in anhydrous dimethylformamide (800 cc) is added 4-phenyl-2-quinolinone (44.3 g). The mixture is heated 1 hour at 120°C. Ethyl 8-bromooctanoate (50.2 g) is then added in solution in anhydrous dimethyl-formamide (250 cc). The mixture is refluxed for 1 hour, cooled on an ice bath, filtered and concentrated to dryness under reduced pressure. The residue is taken up in water (1 litre). The aqueous phase is acidified to pH 4 with acetic acid and extracted with dichloro-methane (3 x 250 cc). The combined organic phases are washed with distilled water until neutrality, dried over sodium sulphate and concentrated to dryness under reduced pressure. After purification by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9-1), the ester thus obtained is treated as in Example 4, but with sodium hydroxide pellets (3 g) dissolved in distilled water (50 cc) and ethanol (500 cc). The product is purified by chromatography under pressure on silica gel (30-60 mm; n-hexane-ethyl acetate 1-1, white solid; m.p.=68°C.)

Example 21

2,2-dimethyl-6-{[4-(4-nitrophenyl)-2-quinolyl]oxy}hexanoic acid

The mixture comprising methyl 2,2-dimethyl-6-{[4-(4-nitrophenyl)-2-quinolyl]oxy}hexanoate (2.95 g) and dry lithium iodide (6.1 g) in 2,4,6-collidine (115 cc) is refluxed, under inert atmosphere, for 1 hour and 30 minutes and then poured in a 2N solution of hydrochloric acid (150 cc) at 0°C. The aqueous phase is extracted with ethyl ether (3 x 50 cc). The combined organic phases are washed with distilled water until neutrality, dried over sodium sulphate and then concentrated to dryness under reduced pressure. The residue obtained is purified by chromatography on silica gel (30-60 mm; n-hexane-ethyl acetate 1-1, white solid; m.p.=85-92°C.)

Example 22

2,2-dimethyl-6-{[4-(4-methylthiophenyl)-2-quinolyl]oxy}hexanoic acid

The suspension obtained by mixing 4-(4-methylthiophenyl)-2-quinolinone (5 g), methyl 6-bromo-2,2-dimethylhexanoate (6.6 g) and potassium carbonate (2.6 g) in dimethylformamide (50 cc) is heated at 100°C for 90 hours. The reaction mixture is then poured in distilled water (400 cc). The aqueous phase is filtered and then extracted with ethyl ether (150 cc). The organic phase is washed with distilled water, dried over sodium sulphate and concentrated to dryness under reduced pressure. Excess methyl 6-bromo-2,2,-dimethylhexanoate is distilled under reduced pressure (bulb distiller; 100°C - 0.1 mbar). After purification by chromatography on silica gel (50-200 mm; dichloromethane), the ester obtained is treated as in Example 20, but with lithium iodide (4.1 g) and 2,4,6-collidine (80 cc). The reaction mixture is refluxed for 3 hours. The product is purified by chromatography on silica gel (50-200 mm; dichloromethane-methanol 98-2) and recrystallization in a dichloromethane-petroleum ether mixture.(yellowish crystals; m.p.=106-107°C.)

Example 23

1-[6-(4-phenyl-2-quinolyloxy)hexanoyl]pyrrolidine

To a solution of 5 g of 6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid in 120 cc of tetrahydrofuran is added 2.9 g of 1,1'-carbonyldiimidazole. The mixture is stirred for 2 hours to 50 C. After cooling, 1.3 g of pyrrolidine is added and the mixture is stirred at room temperature overnight. The tetrahydrofuran is removed in vacuo and the residue partitioned between ethyl acetate and water. The ethyl acetate solution is washed with water, dried (Na_2SO_4), filtered and concentrated in vacuo. The resultant residue is then purified by flash chromatography on silica gel (30-60mm; eluent: 3:7 cyclohexane/ethyl acetate) to give 1-[6-(4-phenyl-2-quinolyloxy)hexanoyl]pyrrolidine as a white solid (m.p.=52-54°C.)

When the procedure of Example 23 is followed and 4-[(4,6-diphenyl-2-pyridyl)oxy]butanoic acid is used in place of 6-[(4-phenyl-2-quinolyl)oxy]-hexanoic acid and aniline is used in place of pyrrolidine, the the product prepared is 4-[(4,6-diphenyl-2-pyridyl)oxy]-butanilide (m.p.=158°C.)

When the procedure of Example 23 is followed and 4-[(4,6-diphenyl-2-pyridyl)oxy]butanoic acid is used in place of 6-[(4-phenyl-2-quinolyl)oxy]-hexanoic acid and DBU and glycine ethyl ester hydrochloride are used in place of pyrrolidine, then the product prepared is ethyl N-[4-(4,6-diphenyl-2-pyridyloxy)-butanoyl]glycinate. (m.p.=93°C.)

Example 24

7-(4-phenyl-2-quinolyl)-6-hepten-1-oic acid

To a suspension of 47.6 g of (6-carboxyhexyl)triphenyl-phosphonium iodide in 600 cc of toluene is added 21.2 g of potassium ter-butylate. The mixture is heated to 90 C for 2 hours under a nitrogen athmosphere. After cooling, to the resultant orange suspension is added a solution of 10 g of 4-phenyl-2-quinolyl-carboxaldehyde (prepared according to the method of E.A. Fehnel,J.O.C. 1966, 31,2899) in 150 cc of toluene. The mixture is stirred for two hours at room temperature and then poured into 800 cc water and the organic layer discarded. The aqueous layer is acidified to pH 5 with 1N hydrochloric acid and extracted with dichloromethane (3x200 cc). The combined extracts are washed with water, dried (Na_2SO_4) and evaporated in vacuo. The residue is flash chromatographed on silica gel (30-60mm; eluent: 92:8 n-hexane/ethyl acetate) and recristallized from 80 cc

acetone to give 7-(4-phenyl-2-quinolyl)-6-hepten-1-oic acid as a whitish solid. (m.p.=152-154°C.)

Example 25

7-(4-phenyl-2-quinolyl)heptanoic acid

A mixture of 1.75 g of 7-(4-phenyl-2-quinolyl)-6-hepten-1-oic acid, 0.18 g of palladium on activated carbon (10% w/w) and 100 cc of tetrahydrofuran is hydrogenated under normal pressure for 1 hour at room temperature. After filtration and concentration in vacuo, the solid residue is stirred in 100 cc diethyl ether and then recristallized from 40 cc acetone to give 7-(4-phenyl-2-quinolyl)eptanoic acid as a whitish solid. (m.p.= 137-139°C).

When the procedure of example 25 is followed and 7-(3-benzyl-phenyl)-6-heptenoic acid is used in place of 7-(4-phenyl-2-quinolyl)-6-hepten-1-oic acid then the product prepared is 7-(3-benzyl-phenyl)eptanoic acid. (m.p.=39°C.)

Example 26

methyl 2,2-dimethyl-6-[(4-phenyl-2-quinolyl)amino]hexanoate

A mixture of 3.2 g of 2-chloro-4-phenyl-quinoline (prepared according to the method of S. Kwon and K. Isagawa, Yoki Gosei Kagaku Shi 1973,31, 313) and 5.9 g of methyl 6-amino-2,2-dimethylhexanoate is heated to 100 C for 8 hours. After cooling, the residue is purified by chromatography on silica gel (eluent: 98:2 dichloromethane/methanol). to give methyl 2,2-dimethyl-6-[(4-phenyl-2-quinolyl)amino]hexanoate obtained as an oil.

Example 27

2,2-dimethyl-6-[(4-phenyl-2-quinolyl)thio]hexanoic acid

methyl 2,2-dimethyl-6-[(4-phenyl-2-quinolyl)thio]hexanoate.

To a solution of 4g of methyl 2,2-dimethyl-6-mercaptohexanoate in 100 cc of dimethylformamide, is added 0.55 g of sodium hydride (50% w/w dispersion in mineral oil). The mixture is stirred for 2 hours until effervescence has stopped. A solution of 5 g of 2-chloro-4-phenylquinoline in 50 cc of dimethyl-formamide is then added. The obtained mixture is heated to 60 C for 8 hours. Ater cooling, 10 cc of methanol is added and the mixture evaporated.

The resultant residue is purified by flash chromatography on silica gel (30-60mm; eluent: 8:2 hexane/ethyl acetate) to give methyl 2,2-dimethyl-6-[(4-phenyl-2-quinolyl)thio]-hexanoate is obtained as an oil.

When the procedure of example 27 is followed and the compounds of Table XVI below are used in place of 2-chloro-4-phenyl-quinoline and the compounds of Table XVII below are used in place of methyl 2,2-dimethyl-6-mercaptohexanoate then the corresponding products are prepared. Representative compounds so prepared are identified in Table XVIII below.

Table XVI

2-chloro-4,5-diphenylpyrimidine
2-chloro-7-methoxy-3-phenylquinoline
2-chloro-4-phenylquinazoline
2-chloro-4-phenylquinoline

Table XVII

methyl 2,2-dimethyl-8-mercaptooctanoate
ethyl 9-mercaptononanoate
ethyl 6-mercaptohexanoate
ethyl 8-mercaptooctanoate
methyl 8-mercaptooctanoate

Table XVIII

2,2-dimethyl-8-(4,5-diphenyl-2-pyrimidylthio)octanoate (colorless oil)
ethyl 9-(4,5-diphenyl-2-pyrimidylthio)nonanoate (colorless oil)
ethyl 6-(4,5-diphenyl-2-pyrimidylthio)hexanoate (colorless oil)
ethyl 8-(4,5-diphenyl-2-pyrimidylthio)octanoate (colorless oil)
ethyl 8-(7-methoxy-3-phenyl-2-quinolylthio)octanoate (colorless oil)
methyl 8-[(4-phenyl-2-quinolyl)thio]octanoate (oil)

Example 28

4-(2-thienyl)-2-quinolinone

To a solution of 2-(2-acetylaminobenzoyl)thiophene (4.8 g) in ethanol (60 cc) is added sodium ethylate (3.2 g). The reaction mixture is refluxed for 9 hours, treated again with sodium ethylate (0.5 g) and then allowed to reflux for 10 hours. The mixture is poured in iced water (200 cc). The precipitate formed is filtered, washed with distilled water until neutrality and then with acetone (3 x 50 cc) and dried at 40°C under reduced pressure. The residue thus obtained is recrystallized in ethanol to obtain the product as a yellow solid. (m.p.=262-264°C.)

Example 29

6-(3,5-diphenyl-phenoxy)hexanoic acid

A. 3,5-diphenyl-anisole

To a mixture of 150 cc of tetrahydrofuran and 34 cc of a 3M solution of phenylmagnesium bromide in diethylether at 40°C under an argon athmosphere, are added 15 g of 3,5-dichloroanisole and 5.5 g of bis(triphenylphosphine)nickel(II) chloride. The resultant black mixture is heated for 6 hours to 65°C and then poured into 400 cc of a saturated aqueous solution of ammonium chloride. After extraction with ethyl acetate (3x150 cc), the combined organic extracts are washed with water, dried ($MgSO_4$) and concentrated in vacuo. The resultant residue is flash chromatographed on silica gel (30-60 mm; eluent: 20:0.1 n-hexane/ethyl acetate) and recristallized from 20 cc of methanol to give 3,5-diphenyl-anisole as a white solid. (m.p.=93-94°C.)

B. 3,5-diphenyl-phenol

A mixture of 4.7 g of 3,5-diphenyl-anisole and 5.3 g of pyridinium hydrochloride was heated for 5 hours to 185°C. After cooling, the residue was partitioned between 100 cc of diethyl ether and 120 cc of water.The organic layer wes then washed with water, dried (Na_2SO_4) and evaporated. The resultant residue was suspended in 50 cc of n-hexane and filtered to give 3.75 g (85%) of 3,5-diphenyl-phenol as a white solid. (m.p.=97°C.)

C. ethyl 6-(3,5-diphenyl-phenoxy)hexanoate

To a suspension of 0.78g of sodium hydride (55 % w/w dispersion in mineral oil) in 300 cc of dimethylformamide was added a solution of 2 g of 3,5-diphenyl-phenol in 10 cc of dimethylformamide. The mixture was stirred for 5 hours at room temperature until effervescence had stopped. 2.2 g of ethyl 6-bromohexanoate was then added and the resultant mixture stirred at room temperature overnight. The mixture was then heated for 20 hours to 40°C. After cooling, the resultant mixture was poured into 100 cc of cold water and extracted with ethyl acetate (3#100 cc). The combined extracts were washed with water, dried (Na_2SO_4) and concentrated in vacuo. The resultant residue was flash chromatographed on silica gel (30-60 mm; eluent: 92:8 n-hexane/ethyl acetate) to give 1 g of ethyl 6-(3,5-diphenyl-phenoxy)hexanoate as a oil, used without further purification in the next step.

D. 6-(3,5-diphenyl-phenoxy)hexanoic acid

By using a similar procedure to that described in example 1 but with 1 g of ethyl 6-(3,5-diphenyl-phenoxy)hexanoate, 0.22 g of potassium hydroxide in pellets, 5 cc of water and 5 cc of ethanol as the starting material (2 hours; reflux), and after recrystallization in a mixture of 10 cc of n-hexane and 2 cc of ethyl acetate, 0.5 g (54%) of 6-(3,5-diphenyl-phenoxy)hexanoic acid was obtained as a white solid. (m.p.=104°C.)

Example 30

6-(4-phenyl-2-quinazolinyloxy)hexanoic acid

To a suspension of 1.74 g of potassium 6-hydroxyhexanoate (prepared from e-caprolactone) in 35 cc of sulfolaneat 60°C was added 0.64 g of sodium hydride (55 % w/w dispersion in mineral oil). The mixture was stirred for 30 minutes to 140°C until effervescence had stopped. 3 g of 2-chloro-4-phenyl-quinazoline were then added and the resultant mixture was heated for further 2 hours to 140°C. The mixture was poured into 500 cc of water, neutralized with acetic acid and extracted with dichloromethane (3#300 cc). The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (50-200 mm; eluent: 95:5 diethyl ether/methanol), then washed with n-hexane and filtered to give 0.4 g (10%) of 6-(4-phenyl-2-quinazolinyloxy)hexanoic acid as a whitish solid.(m.p.=112-114°C.)

Example 31

7-(3-benzyl-phenyl)6-heptenoic acid

By using a similar procedure to that described in example 24 but with 1 g of 3-benzylbenzaldehyde, 5.5 g of (6-carboxy-hexyl)triphenylphosphonium iodide, 2.5 g of potassium ter-butylate and 40 cc of toluene as the starting material (1 hour; 50°C.), and after purification by flash chromatography on silica gel (30-60Mm; eluent: 8:2:0.05 n-hexane/ethyl acetate/acetic acid), 7-(3-benzyl-phenyl)-6-heptenoic acid is obtained. (m.p.=68°C.)

The starting 3-benzyl-benzaldehyde is prepared in an analogous manner that is described for 3,5-diphenyl-anisole in example 29 but with 23 g of 2-(3-bromophenyl)-1,3-dioxolan in place of 3,5-dichloroanisole, 62 cc of a 3M solution of benzylmagnesium bromide in terahydrofuran in place of a 3M solution of phenylmagnesium bromide in diethylether, 0.87g of bis(triphenylphosphine)-nickel(II) chloride and 200 cc of tetrahydrofuran as the starting material, followed by a deprotection step with a mixture of 46 g of silica gel (50-200 mm), 4.6 cc of a 10% aqeous solution of oxalic acid in 250 cc of dichlorometahne, results in 3-benzyl-benzaldehyde. (whitish solid-oil).

Example 32

methyl 2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate.

The procedure in Example 4 is followed but using 4,6-diphenyl-2-pyridinone (4 g), methyl 6-bromo-2,2-dimethylhexanoate (5.8 g) (prepared according to the method described in Patent EP 108 592), silver carbonate (2.3 g) and toluene (150 cc). The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 95-5, brown oil)

Example 33

2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid.

The procedure in Example 6 is followed but using methyl 2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl) oxy]hexanoate (5 g), potassium hydroxide pellets (1.1 g) and ethanol (100 cc). The reaction mixture is refluxed for

24 hours. The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 8-2), white crystals (m.p.=115°C.)

Example 34

methyl 2-ethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate.

The procedure in Example 5 is followed but using 4,6-diphenyl-2-pyridinone (2.8 g) (prepared by analogy with the method described in Patent EP 108 592 from methyl butanoate), methyl 6-bromo-2-ethylhexanoate (5.4 g), silver carbonate (1.6 g) and dimethylformamide (100 cc). The reaction mixture is heated at 100°C for 31 hours then at 120°C for 40 hours. The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9-1). (yellow oil)

Example 35

2-ethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid.

The procedure in Example 6 is followed but using methyl 2-ethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (3.15 g), potassium hydroxide pellets (0.9 g) dissolved in distilled water (20 cc) and ethanol (100 cc). The reaction mixture is refluxed for 8 hours. The product is purified by recrystallisation in an n-hexane-ethyl acetate (2-1) mixture (40 cc), white crystals (m.p.=115°C.)

Example 36

ethyl 2-ethyl-2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate.

The procedure in Example 5 is followed but using 4,6-diphenyl-2-pyridinone (3 g), ethyl 6-bromo-2-ethyl-2-methylhexanoate (6.44 g) [prepared according to the method of K.E. MOELLER, Brenstoff-Chem., 47, 10 (1966)], silver carbonate (1.68 g) and dimethylformamide (110 cc). The reaction mixture is heated at 100°C for 121 hours. The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9-1).(yellow oil)

Example 37

2-ethyl-2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid.

The procedure in Example 6 is followed but using ethyl 2-ethyl-2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate (3.6 g), potassium hydroxide pellets (0.95 g) dissolved in distilled water (20 cc) and ethanol (50 cc). The reaction mixture is refluxed for 120 hours. The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 75-25) and then by recrystallisation in an n-hexane-ethyl acetate (2-1) mixture (40 cc), white crystals (m.p.=119-120°C.)

Example 38

ethyl 2-methyl-6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}-hexanoate.

The procedure in Example 5 is followed but using 4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridinone (2.5 g), ethyl 6-bromo-2-methylhexanoate (4 g), silver carbonate (1.2 g) and dimethylformamide (100 cc). The reaction mixture is heated at 100°C for 72 hours. The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9-1). (yellowish oil)

Example 39

2-methyl-6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid.

The procedure in Example 6 is followed but using ethyl 2-methyl-6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoate (2.6 g), potassium hydroxide pellets (0.5 g) dissolved in distilled water (10 cc) and ethanol (150 cc). The reaction mixture is refluxed for 4 hours. The product is purified by recrystallisation in an n-hexane-ethyl acetate (5-3) mixture (80 cc).white crystals. (m.p.=123-125°C.)

Example 40

2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile.

The procedure in Example 4 is followed but using 4,6-diphenyl-2-pyridinone (6.3 g), 6-bromo-2,2-dimethylhexanonitrile (2.60 g) (prepared according to the method of M. Larchevêque et al., Bull. Soc. Chim. Fr., 1710

(1974)), silver carbonate (3.5 g) and toluene (300 cc). The product is purified by chromatography under pressure on silica gel (30-60 mm); eluent: n-hexane-ethyl acetate 9.5-0.5).yellowish solid. (m.p.=71°C.)

Example 41

5-[1,1-dimethyl-5-[(4,6-diphenyl-2-pyridyl)oxy]pentyl]-[1H]-tetrazole.

The procedure in Example 9 is followed but using 2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanonitrile (3.5 g), sodium nitride (2.4 g), ammonium chloride (2 g) and dimethyl formamide (40 cc). The reaction mixture is heated at 120°C for 96 hours. The product is purified by chromatography under pressure on silica gel (30-60 mm; eluent: n-hexane-ethyl acetate 9-1). The solid residue obtained is taken up in ethyl ether (100 cc). After stirring for 1 hour at room temperature, the solid is separated by filtration, washed with ethyl ether (3 30 cc) and then dried under reduced pressure, white solid. (m.p.=160-162°C.)

Example 42

In some cases, various stereoisomeric products may exist. This invention is not limited to any particular stereoisomer but includes all possible individual isomers and mixtures thereof. The stereoisomers of the compounds of this invention can be separated according to standard methods known in the art, for example directly by chromatography on chiral support or by separation of pure diastereoisomeric precursors. For example, the N-[6-(4,6-diphenyl-2-pyridyloxy)-2-methylhexanoyl]-(1R,5S)-10,2-camphorsultam can be obtained by adding dropwise a solution of 1.8 g of 6-(4,6-diphenyl-2-pyridyloxy)-2-methylhexanoyl chloride in 10 cc of toluene to a mixture of 2 g of (+)-10,2-camphorsultam and 0.44 g of sodium hydride (50% w/w dispersion in mineral oil) in 20 cc of toluene. The obtained mixture is stirred overnight. After adding 70 cc of water, the mixture is extracted with toluene (3x70 cc). The combined extracts are dried over magnesium sulfate, filtered and evaporated to give 0.7 g of the expected diastreoisomeric mixture (50/50). The diastereisomers can be separated by high liquid pressure chromatography on chiral support CHIRACEL OD; 1 ml/mn; P=49 bars; eluent: 95:5 heptane/ethanol; retention times: 9.84 and 12.0l mn respectively). The pure stereoisomeric 6-(4,6-diphenyl-2-pyridyloxy)-2-methyl-hexanoic acids can be prepared from the pure

previously described diastereoisomers by saponification, according to the method of W. (ppolzer et al., Tetrahedron Letters, 1989, 30, 5603 and 6009.

Compounds within the scope of the present invention have potent activity as leukotriene B_4 antagonists and as such possess therapeutic value in the treatment of inflammatory conditions and hypersensitivity responses. LTB_4 is implicated in diseases such as rheumatoid arthritis, gout, psoriasis and inflammatory bowel disease and therefore compounds which demonstrate LTB_4 antagonist properties are useful in the control of these disease states. Compounds of general formula I and their salts are also particularly useful in the osteoarticulatory field. By virtue of their affinity for leukotriene B_4 receptors, they interfere with this agonist by blocking its action at the receptor level.

Their affinity for leukotriene B_4 receptors has been successfully demonstrated by measuring their effect on the binding to tritium-labelled leukotriene B_4 using guinea-pig spleen membranes, according to a method inspired by the method of J.B. Cheng, J. of Pharmacology and Experimental Therapeutics, 236, 126 (1986). In this technique, compounds according to the invention are active at concentrations of between about 0.5 to about 5,000 nM (IC_{50}). Further, compounds of this invention are shown to be leukotriene B_4 antagonists in the technique of guinea-pig pulmonary parenchyma contraction antagonism induced by LTB_4 described by P. Sirois et al., Pharmacology, 31, 225-236 (1985). In this technique, products are active at concentrations of between about 1 to about 10,000 nM. When compounds of this invention are used in these tests it can be shown that they are considered to be active as leukotriene B_4 antagonists. The results of representative compounds so tested are shown below in Table XIX.

Table XIX

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid	3	300
2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]-hexanoic acid	5	10
7-[(4,6-diphenyl-2-pyridyl)oxy]heptanoic acid	25	1300
5-[(4,6-diphenyl-2-pyridyl)oxy]pentanoic acid	50	2000
4-[(4,6-diphenyl-2-pyridyl)oxy]butanoic acid	300	

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
2,2-dimethyl-7-[(4,6-diphenyl-2-pyridyl)oxy]-heptanoic acid	15	30
2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid	4	10
2-ethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid	3	70
2-ethyl-2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]-hexanoic acid	17	30
2,2-dimethyl-8-[(4,6-diphenyl-2-pyridyl)oxy]octanoic acid	22	
methyl 6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoate	40	>10000
6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	10	1000
2,2-dimethyl-6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	100	
ethyl 6-{[6-(4-chlorophenyl)-4-phenyl-2-pyridyl]-oxy}hexanoate	5000	
6-{[6-(4-chlorophenyl)-4-phenyl-2-pyridyl]oxy}-hexanoic acid	1000	
6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	15	1100
2,2-dimethyl-6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	50	170
2-methyl-6-{[4-(4-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	4	20
6-{[6-(4-methoxyphenyl)-4-phenyl-2-pyridyl]oxy}-hexanoic acid	1000	
6-{[6-(4-trifluoromethylphenyl)-4-phenyl-2-pyridyl]-oxy}hexanoic acid	1200	
6-{[4,6-di(4-chlorophenyl)-2-pyridyl]oxy}hexanoic acid	1200	
6-{[6-(4-methylphenyl)-4-phenyl-2-pyridyl]oxy}-hexanoic acid	300	
6-{[6-(4-chlorophenyl)-4-(4-methoxyphenyl)-2-pyridyl]oxy}hexanoic acid	1200'	>10000

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
6-{[4-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-pyridyl]oxy}hexanoic acid	1700	
6-{[4-(2-fluorophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	10	1700
6-{[6-phenyl-4-(4-trifluoromethylphenyl)-2-pyridyl]-oxy}hexanoic acid	110	
6-{[4-(3-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	8	200
2,2-dimethyl-6-{[4-(3-Methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	2	30
6-{[4,6-di(4-methoxyphenyl)-2-pyridyl]oxy}hexanoic acid	3000	
6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	3	800
2,2-dimethyl-6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid.	7	300
6-{[6-(4-fluorophenyl)-4-phenyl-2-pyridyl]oxy}-hexanoic acid	30	1700
6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}-hexanoic acid	3	60
6-{[6-(3-methoxyphenyl)-4-phenyl-2-pyridyl]oxy}-hexanoic acid	500	
6-{[4-(3,4-dichlorophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	500	
6-{[4-(4-methylphenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	15	100
6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	4	
sodium 6-{[6-(2-chlorophenyl)-4-phenyl-2-pyridyl]-oxy}hexanoate	1.8	200
6-{[4-(2-chlorophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	200	
2-methyl-6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	5.5	1000

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
2-methyl-6-{[4-(4-chlorophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	5.5	70
2,2-dimethyl-6-{[4-(3-chlorophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	13	1000
2-methyl-6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]-oxy}hexanoic acid	4	6
2,2-dimethyl-6-{[6-(2-fluorophenyl)-4-phenyl-2-pyridyl]oxy}hexanoic acid	5	80
6-{[6-(3-fluorophenyl)-4-phenyl-2-pyridyl]oxy}-hexanoic acid	4	150
6-{[4-[3-fluorophyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	3	200
2-methyl-6-{[4-(4-fluorophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	1.7	60
6-{[4-(4-fluorophenyl)-6-(2-fluorophenyl)-2-pyridyl]-oxy}hexanoic acid	10	1000
2-methyl-6-{[4-(3-methoxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid.	5	20
6-{[4-(4-methylthiophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	10	3000
6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	1	5
2-methyl-6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	7	2.5
2,2-dimethyl-6-{[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	7	140
6-{[4-(3-methylphenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	15	
2-methyl-6-{[4-(4-methylphenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	13	20
6-{[4-(4-dimethylaminophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	30	6000
6-{[4-(4-nitrophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	50	

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
6-{[4-phenyl-6-(2-thienyl)-2-pyridyl]oxy}hexanoic acid	50	300
2,2-dimethyl-6-{[4-phenyl-6-(2-thienyl)-2-pyridyl]-oxy}hexanoic acid	15	1000
6-{[4-phenyl-6-(3-thienyl)-2-pyridyl]oxy}hexanoic acid	10	1000
2,2-dimethyl-6-{[4-phenyl-6-(3-thienyl)-2-pyridyl]-oxy}hexanoic acid	5	100
6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid	700	
2-methyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid	550	
2,2-dimethyl-6-[(4-phenyl-2-quinolyl)oxy]hexanoic acid	150	
2-ethyl-2-methyl-6-[(4-phenyl-2-quinolyl)oxy]-hexanoic acid	110	
7-[(4-phenyl-2-quinolyl)oxy]heptanoic acid	1800	
8-[(4-phenyl-2-quinolyl)oxy]octanoic acid	2000	
6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}hexanoic acid	30	
2-methyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}-hexanoic acid	30	
2-ethyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}-hexanoic acid	200	
2,2-dimethyl-6-{[4-(4-chlorophenyl)-2-quinolyl]oxy}-hexanoic acid	15	
2,2-dimethyl-6-{[4-(3-chlorophenyl)-2-quinolyl]oxy}-hexanoic acid	1100	
2,2-dimethyl-6-{[4-(2-fluorophenyl)-2-quinolyl]oxy}-hexanoic acid	800	
2,2-dimethyl-6-{[4-(4-fluorophenyl)-2-quinolyl]oxy}-hexanoic acid	150	
2,2-dimethyl-6-{[4-(3,4-dichlorophenyl)-2-quinolyl]-oxy}hexanoic acid	3500	
2,2-dimethyl-6-[(6-chloro-4-phenyl-2-quinolyl)oxy}-hexanoic acid	2500	
2,2-dimethyl-6-[(7-chloro-4-phenyl-2-quinolyl)oxy}-hexanoic acid	2000	

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
2,2-dimethyl-6-{[4-(4-nitrophenyl)-2-quinolyl]oxy}-hexanoic acid	150	
2,2-dimethyl-6-{[4-(3-methoxyphenyl)-2-quinolyl]-oxy}hexanoic acid	300	
2,2-dimethyl-6-{[4-(4-methoxyphenyl)-2-quinolyl]-oxy}hexanoic acid	10	
2-methyl-6-{[4-(4-methoxyphenyl)-2-quinolyl]oxy}-hexanoic acid	16	
2,2-dimethyl-6-{[4-(3-tolyl)-2-quinolyl]oxy}hexanoic acid	3500	
2,2-dimethyl-6-{[4-(4-tolyl)-2-quinolyl]oxy}hexanoic acid	30	
2,2-dimethyl-6-[(7-methyl-4-phenyl-2-quinolyl)oxy]-hexanoic acid	2000	
2,2-dimethyl-6-{[4-(4-trifluoromethylphenyl)-2-quinolyl]oxy}hexanoic acid	300	
2,2-dimethyl-6-{[4-(4-dimethylaminophenyl)-2-quinolyl]oxy}hexanoic acid	30	
2,2-dimethyl-6-{[4-(2-thienyl)-2-quinolyl]oxy}-hexanoic acid	200	
6-[(4,6-diphenyl-2-pyridyl)oxy]hexanamide	160	>10000
5-{[5-(4,6-diphenyl-2-pyridyl)oxy]pentyl}-[1H]-tetrazole	10	10
5-{1,1-dimethyl-5-[(4,6-diphenyl-2-pyridyl)oxy]-pentyl}-[1H]-tetrazole	7	20
5-{5-[(4-phenyl-2-quinolyl)oxy]pentyl}-[1H]-tetrazole	500	
5-{1,1-dimethyl-5-[(4-phenyl-2-quinolyl)oxy]pentyl}-[1H]-tetrazole	400	
5-{1,1-dimethyl-5-{[4-(4-chlorophenyl)-2-quinolyl]-oxy}pentyl}-[1H]-tetrazole	30	
5-{5-{[4-(4-chlorophenyl)-2-quinolyl]oxy}pentyl}-[1H]-tetrazole	25	
Sodium 2-{3-[(4,6-diphenyl-2-pyridyl)oxy]propyloxy}-acetate	100	

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	2	40
2-methyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	5	20
2,2-dimethyl-6-{[4-(4-aminophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	10	1
6-{[4-(3-aminophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	12	
2,2-dimethyl-6-{[4-(4-aminophenyl)-2-quinolyl]-oxy}hexanoic acid	40	
6-{[4-(4-methylaminophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	5	150
6-{[4-(4-isopropylaminophenyl)-6-phenyl-2-pyridyl]-oxy}hexanoic acid	22	
6-{[4-(4-benzamidophenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid	4000	
6-{[4-(4-trifluoroacetamidophenyl)-6-phenyl-2-pyridyl]oxy}hexanoic acid	150	
6-{[4-(4-methylaminophenyl)-6-phenyl-2-pyridyl]-oxy}-2,2-dimethyl-hexanoic acid	8	
6-{[6-(2-chlorophenyl)-4-(3,4-methylenedioxy-phenyl)-2-pyridyl]oxy}-2-methylhexanoic acid	2	
5-{5-{[6-phenyl-4-(3,4-methylenedioxyphenyl)-2-pyridyl]oxy}pentyl}-1H-tetrazole	2	
2,2-dimethyl-6-[(3-methyl-4-phenyl-2-quinolyl)oxy]-hexanoic acid	8000	
6-[(4-phenyl-2-pyridyl)oxy]hexanoic acid	900	
6-[(4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid	40	3000
6-{[4-(4-chlorophenyl)-2-pyridyl]oxy}-2,2-dimethyl-hexanoic acid	20	
6-[(6-ter-butyl-4-phenyl-2-pyridyl)oxy]hexanoic acid	300	2000
6-[(6-ter-butyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethyl-hexanoic acid	40	1000
6-[(6-methyl-4-phenyl-2-pyridyl)oxy]hexanoic acid	200	

Compound	IC_{50}/nM Binding (Cheng)	L. Parenchyma
6-[(6-methyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethyl-hexanoic acid	10	
6-[(6-cyclopropyl-4-phenyl-2-pyridyl)oxy]hexanoic acid	40	
6-[(6-cyclopropyl-4-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid	4	200
6-[(6-methyl-4-phenyl-2-quinolyl)oxy]-2,2-dimethyl-hexanoic acid	5000	
4-[(4,6-diphenyl-2-pyridyl)oxy]butanilide	>1000	
4-[(4,6-diphenyl-2-pyridyl)oxymethyl]benzoic acid	350	10000
N-[4-(4,6-diphenyl-2-pyridyloxy)butanoyl]glycine	16	
6-[(4,6-diphenyl-2-pyrimidyl)oxy]hexanoic acid	150	
6-[(4,6-diphenyl-2-pyrimidyl)oxy]-2,2-dimethyl-hexanoic acid	10	1000
6-[(5,6-diphenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid	10000	
sodium 8-[(5,6-diphenyl-2-pyridyl)oxy]octanoate	10000	
8-{[5,6-bis-(4-methoxyphenyl)-2-pyridyl]oxy}octanoic acid	3000	
6-[(6-phenyl-2-pyridyl)oxy]-2,2-dimethylhexanoic acid	2000	
sodium 8-[(6-phenyl-2-pyridyl)oxy]octanate	6000	
2,2-dimethyl-8-(4,5-diphenyl-2-pyrimidylthio)-octanoic acid	2500	
8-(4,5-diphenyl-2-pyrimidyloxy)octanoic acid	8500	
6-[4,5-bis-(4-methoxyphenyl)-2-pyrimidyloxy]-hexanoic acid	8000	
6-(4,5-diphenyl-2-pyrimidylthio)hexanoic acid	8000	
sodium 8-(4,5-diphenyl-2-pyrimidylthio)octanoate	3000	
6-(3,5-diphenyl-phenoxy)hexanoic acid	8	
7-(3-benzyl-phenyl)6-heptenoic acid	10000	
7-(3-benzylphenyl)heptanoic acid	7000	
sodium 8-(4-phenyl-2-quinazolylthio)octanoate	9000	

Compound	Binding (Cheng) % Inhibition at 10 μM
1-[6-(phenyl-2-quinolyloxy)hexanoyl]pyrrolidine	12
7-(4-phenyl-2-quinolyl)-6-hepten-1-oic acid	27
7-(4-phenyl-2-quinolyl)heptanoic acid	36
2,2-dimethyl-6-[(4-phenyl-2-quinolyl)thio]-hexanoic acid	33
6-{[4-(2-methoxyphenyl)-2-quinolyl]oxy}-2,2-dimethylhexanoic acid	36
6-[(6-methoxy-4-phenyl-2-quinolyl)oxy]hexanoic acid	30
sodium 8-[(4-phenyl-2-quinolyl)thio]octanoate	31
6-{[6-phenyl-4-(3,4-dimethoxyphenyl)-2-pyridyl]-oxy}hexanoic acid	21
6-{[6-phenyl-4-(4-carboxyphenyl)-2-pyridyl]oxy}-hexanoic acid	32
6-{[6-phenyl-4-(3,5-dimethoxyphenyl)-2-pyridyl]-oxy}hexanoic acid	50
6-[(5,6-diphenyl-2-pyridyl)oxy]hexanoic acid	15
6-{[5,6-bis-(4-methoxyphenyl)-2-pyridyl]oxy}-hexanoic acid	37
6-[4,5-bis-(4-chlorophenyl)-2-pyrimidyloxy]hexanoic acid	48
7-(4,5-diphenyl-2-pyrimidyloxy)heptanoic acid	22
6-(4,5-diphenyl-2-pyrimidyloxy)hexanoic acid	35

Furthermore, compounds within the scope of this invention have the advantage of being of very low toxicity. As demonstrated in mice, toxicity is generally greater than 200 mg/kg by the oral route.

Further tests can be used to determine the effectiveness of compounds of this invention such as the following. The LTB_4 guinea pig polymorphonuclear membrane binding assay can be used to determine compounds exhibiting LTB_4 receptor binding properties. Compounds active in this assay can then be subjected to the guinea pig peritoneal PMN LTB_4-induced aggregation assay. THE LTB_4-induced aggregation assay

determines the antagonistic activity of a compound. The guinea pig LTB_4-induced wheal assay is used to determine in vivo activity.

Assay for Inhibitors of (^{3}H)-LTB_4 Binding to Membranes From Guinea Pig Polymorphonuclear Leukocytes

Preparation of test compounds

Dissolve compounds to a concentration 100-fold higher than the highest desired concentration for testing. Serially dilute the compound so that all dilutions are 100-fold higher than the assay concentration desired. Compounds are typically dissolved in DMSO. If compounds are insoluble in DMSO, solutions are heated or sonicated to induce solubilization. Compounds may also be dissolved in ethanol.

Final assay concentrations of DMSO and ethanol can be as high as 1.0% and 2.0% (v/v); these concentrations have no measurable effects on specific binding.

Preparation of the membrane receptor fraction

To obtain polymorphonuclear leukocytes (PMNs), 25-30 male Hartley guinea pigs (250-350g) are intraperitoneally injected with 6 mls of an 8% sodium caseinate solution. 18 to 24 hours later, the guinea pigs are sacrificed by decapitation. The peritoneal cavity is lavaged with 15 mls of isolation buffer. The cells are collected and centrifuged at 200xg for 10 minutes. Contaminating red blood cells can be removed by hypotonic lysis. The cells are resuspended in isolation buffer and centrifuged as before. They are filtered through gauze and centrifuged again. The resulting pellet is suspended in 3 ml of sonication buffer, counted and brought to a concentration of 1×10^8 cells/ml. This suspension is lysed on ice with 5 bursts of 30 seconds separated by 1 minute intervals. The homogenate is centrifuged at 200xg for 10 minutes at 4°C. Aliquots of supernatant are transferred to high speed centrifuge tubes (1 tube per 3 guinea pigs). The tubes are centrifuged at 49,000xg for 15 minutes at 4°C. The pellets are resuspended by three 5 second bursts of sonication, separated by 20 second intervals. This suspension is centrifuged at 50,000xg for 20 minutes at 4°C. Pellets are stored at -70°C for up to 3 months.

To use in the binding assay, the pellet is thawed at room temperature and suspended in 9 mls of assay buffer (sonication may be necessary).

Binding assay

Each assay tube (16 x 100 mm) contains the following:

345 ml Assay Buffer
5 ml Test compound or solvent
50 ml ^{3}H-LTB$_4$ (0.50 nM)
100 ml Protein preparation (0.2 mg)

Incubations are done at 30°C for 40 minutes in a water bath. Reactions are started by the addition of (^{3}H)-LTB$_4$ solution. Samples are collected via a Brandel M24 Harvester for binding assays. Tubes should be washed with a total of 19 ml cold wash buffer.

The filters are transferred to 7 ml plastic scintillation vials to which 6.0 ml of appropriate scintillation fluid (e.g., Scintiverse®) is added. After being allowed to equilibrate for 12 hours, the radioactivity is counted with a liquid scintillation counter appropriately set for tritium.

The required control assay tubes include the following:

(a) Total Binding: No test compound is added; buffer is substituted.

(b) Non-Specific Binding: Non-labeled ligand is added at a concentration of 1 mM.

(c) Solvent Controls: If test compound is dissolved in a solvent, controls for both Total Binding and Non-Specific Binding containing solvent but no compounds are required.

Calculations:

Specific binding is defined as that amount of radioligand prevented from binding by 1000-fold excess non-labeled ligand, i.e., total binding minus non-specific binding. This operational definition is verified by Scatchard analysis of total binding.

Inhibition of specific binding is defined as the decrease in specific binding caused by the test compound,

$$\frac{SB_C - SB_T}{SB_C} \times 100$$

where SB_C is the specific binding in the absence of test compound and SB_T is the specific binding in the presence of test compound. The I_{50} values (concentrations required to inhibit specific binding by 50%) are determined by graphic analysis of the specific binding observed in the presence of various concentrations of test compound.

The results of this test indicate that compounds of this invention exhibit valuable LTB_4 receptor binding properties which are useful in the treatment of inflammatory conditions and hypersensitivity responses.

LTB_4-Induced Wheal Formation in Guinea Pig

LTB_4 plays the role of a mediator in cellular induced inflammation. The induction of chemokinesis and chemotaxis of PMNs and macrophage by LTB_4 have contributed to its association with the vascular aspects of acute inflammatory reactions.

In this test intradermal injection of 0.1 ml of a 10 mg/ml solution of LTB_4 to guinea pig back skin causes the formation of a wheal. This wheal is visualized by the prior intravenous injection with the indicator 1% Evan's Blue dye. Following a 2 hour incubation post-LTB_4 challenge, the guinea pigs are euthanized via CO_2 asphyxiation. Their dorsal skins are reflected and the diameters of the challenged sites are compared with those of the vehicle control injected sites.

Preparation and handling of guinea pigs

The guinea pigs must be quarantined 5 to 7 days prior to the study. The day before the test, the back and hind limbs are shaved taking care not to nick the skin. After shaving, the guinea pigs are fasted, but water is provided.

On the day of the test, the guinea pigs are weighed and identified with an ink mark designating them with numbers 1 through 5 in each group. Groups are formed by random distribution.

Preparation and route of administration of compounds

The oral vehicles are Polyethylene Glycol (PEG 400) (2 ml/kg) and methocel (0.5% w/v) (10 ml/kg). Exposure to the ultrasound of a Branson sonicator assures uniformity of suspension or dissolution of the test compounds. Compounds for parenteral administration are dissolved in saline with the assistance of 0.1N HCl and 0.1N NaOH and then adjusting the pH to near neutrality.

Although test compounds are usually administered orally, other routes of administration such as intravenous, intraperitoneal or subcutaneous may be used.

Preparation of leukotriene B_4 for intradermal injection

LTB_4 is obtained as a stock solution (50 mg/ml) in ethanol and is stored at -80°C until required for use. The stock solution or an appropriate aliquot is transferred from the ampule into a 10 ml glass vial using a pasteur pipette. The stock solution is then evaporated to dryness under a slow, steady stream of argon gas.

A solution of freshly prepared 0.25% Bovine Albumin in Phosphate-Buffered Saline is bubbled with argon gas until the saturation point is reached (approximately 5 minutes). This argon-saturated vehicle is then used to reconstitute the evaporated LTB_4 stock residue to yield a final working concentration of 10 mg/ml. The rubber stoppered vial of LTB_4 working solution is kept on wet ice during the study.

Preparation of Evan's Blue dye solution

Because Evan's Blue is an easily visible marker that binds to the plasma proteins, it has been selected to assist the investigator in the measurement of the wheals induced during the study. Evan's Blue Dye is dissolved as a 1% w/v solution in 0.9% w/v physiologic saline. The number of 1 ml plastic disposable syringes, fitted with 27 gauge, 1/2 inch needles and filled with the 1% dye solution, is determined by the number of animals expected to be included in the study.

Conduct of an experiment

Test compounds or their appropriate controls are administered orally with 16 gauge, 3 inch dosing cannulas. Immediately after dosing, the guinea pig is injected intravenously with 1 ml of 1% Evan's Blue Dye into a digital vein in the left or right shaved hind limb. This injection is facilitated best through the use of a 1 ml plastic syringe fitted with a 27 gauge, 1/2 inch needle. Immediately following Evan's Blue injection, the guinea pig is injected intracutaneously at each of 2 sites in the shaved dorsal midline with 0.1 ml of the prepared argon-saturated LTB_4 solution (1 mg/0.1 ml). A third site is intracutaneously injected with the argon-saturated 0.25% bovine albumin in phosphate-buffered saline to serve as a vehicle control.

2 hours after challenge, the guinea pigs are euthanized by inhalation of carbon dioxide. Carbon dioxide is administered by inserting a rubber tube from the tank into a plastic bag containing the caged group of guinea pigs. Asphyxiation occurs in approximately 5 minutes.

After death, the dorsal skins are reflected to enable the measurement of 2 perpendicular diameters of the resultant wheals. The area of each wheal is determined using the formula: Area = πr^2.

Calculations and statistics

For each guinea pig, the mean of the wheal areas obtained for the 2 injections sites is established after correction is made for the effect of the wheal area induced by the 0.25% Bovine Albumin in Phosphate-Buffered Saline vehicle. Then, a mean area for each treatment group with its corresponding standard error is calculated.

The following equation is used to calculate the percent inhibition of vehicle treated control wheal area by treatment with test compound:

$$\frac{\text{Mean Wheal Area}_{[\text{Control}]} - \text{Mean Wheal Area}_{[\text{Treated}]}}{\text{Mean Wheal Area}_{[\text{Control}]}}$$

In multiple dose experiments, the dose of a test compound that will cause 50% inhibition (ED_{50}) can be calculated from the regression equation

for the response as percent inhibition (y) and log dose (x) and estimating the (ED_{50}) from: $\hat{y}(50) = bx + m$ where:

$\hat{y}$ = 50% inhibition,

x = dose of test compound,

b = slope of dose response line and

m = intercept of the dose response line.

95% confidence limits of ED_{50} are calculated from the regression equation by the method of Litchfield and Wilcoxon where:

$ED_{25} = \hat{y}(25) = bx + m$,

$ED_{75} = \hat{y}(75) = bx + m$ and

$$S = \frac{(ED_{75}/ED_{50}) + (ED_{50}/ED_{25})}{2}$$

where S is the slope function used to compute the limit factor fED_{50} $2.77/\sqrt{N}$ as $fED_{50} = S$. 2.77 is an estimator, N is the square root of the number of animals used for all the doses and fED_{50} is the factor to determine the upper (RU) and lower (RL) limits of the ED_{50} as: $RU = ED_{50} \times fED_{50}$ and $RL = ED_{50} \div fED_{50}$. Statistical significance of any inhibition caused by treatment with a test compound can be calculated by applying Student's t (two-tailed) to the data.

Validation and specificity studies

The 1 mg/0.1 ml/site challenge dose of LTB_4 was selected for the reproducibility, sensitivity and ease of measurement of the resultant wheal. Studies have indicated that size of wheals induced by LTB_4 is directly related to the dose administered.

2 hours of incubation after intradermal challenge with LTB_4 was selected as the routine timing for the study. Duration studies conducted evidenced the production of measurable, reproducible wheals at the 2 hour endpoint.

In view of the results obtained when compounds of the present invention are subjected to this test, it can be demonstrated that valuable properties as LTB_4 antagonists are indicated.

A further test which may be used to determine the ability of compounds of this invention to exhibit LTB_4 antagonist activities is as follows:

Guinea Pig Polymorphonuclear Leukocyte Aggregation Assay

Isolation of guinea pig PMNs

6 ml of 6% Na-caseinate (in saline) is injected intraperitoneally into 2 male guinea pigs (250-300g) lightly anesthetized with CO_2 or ether. The following day (18-24 hours post injection) the animals are sacrificed by decapitation or CO_2 overdose according to the SOP for nonclinical laboratory study methods.

A midline section of abdominal skin is removed and 13 ml Hanks buffer (containing 500 ml 10 mM EDTA/500 ml Hanks) plus 2 ml 7% Na-citrate is injected into the peritoneal cavity. The guinea pig is rocked back and forth 5 times. A small incision is made on the left side of the midline of the abdominal wall (avoid cutting obvious blood vessels). Use a fire-polished pasteur pipette to transfer the buffer plus cells from the abdominal cavity to 2 washed Nalgene (Oak Ridge) centrifuge tubes (half of buffer and cells in each tube). The tubes are then filled to 50 ml with additional citrate-Hanks buffer and centrifuged at 4000 rpm for 10 minutes.

Each pellet is resuspended in 1 ml of citrate-Hanks and then diluted to 50 ml with the same buffer. The cells are incubated for 30 minutes at room temperature on a Hema-Tek aliquot mixer. The cells are filtered through 2 layers of gauze into 50 ml with plastic beakers to remove PMN aggregates and then transferred to fresh, washed, 50 ml Nalgene centrifuge tubes.

The cells are centrifuged for 5 minutes, resuspended in 50 ml of fresh buffer, centrifuged again and then resuspended in 3 ml of citrate-free Hanks buffer. (Following any centrifugation the cells are always resuspended first in 1 ml of the desired fresh buffer.)

An aliquot of the washed cells, diluted 50-fold, is counted using a microscope and a hemacytometer.

The PMNs are counted as follows:

1. Dilute 50 ml of cells into 450 ml of Hank's buffer.

2. Dilute 50 ml of (1) with 150 ml of Hank's buffer plus 50 ml of Toluidine blue (50x total dilution). Add 10 ml of (2) to the hemacytometer and count cells in 16 large squares (volume counted = 1 ml). View the hemacytometer under 40x magnification. The unstained cells are PMNs.

Calculation: assume 149 cells are counted.

$$\frac{\text{\# of cells counted/ml x dilution factor x 2 ml}}{\text{desired final cell concentration}} = \text{Final volume of buffer needed/ml of cells}$$

cells/ml = 149/.0001 = 1,490,000 cells/ml

$$\frac{1.49 \times 10^6 \times 50 \times 1}{3 \times 10^7} = \frac{7.45 \times 10^8}{3 \times 10^7} = 2.48 \text{ ml/ml of cells counted}$$

Thus, cells must be diluted 2.48-fold with Hanks buffer (2.48 x 3 = 7.44 ml; 7.44 - 3.0 = 4.44; add 4.44 ml buffer to the 3 ml of washed cells). This results in 7.44 ml of cells at a concentration of 3×10^7 cells per ml.

Instrument adjustments

Place cuvettes containing 1×10^7 cells/ml (166 ml PMNs plus 334 ml buffer) plus flea magnets in the aggregometer sample wells. Turn on the Chart Advance to 30 cm/hr. Turn the attenuation dials to mid range and decrease the recorder mV range settings to 50 mV full scale. Press the red "zero" button on the aggregometer and note exactly the position of the recorder pens. Turn the aggregometer left hand "PPP" dials for each cuvette position to the left or right so that the associated recorder pens move to the exact positions noted by pressing the red "zero" button. The electrical circuits are now "balanced". Except for small balance adjustments, do not make any further changes in pen positions by adjusting the "PPP" dials.

Withdraw one of the cuvettes from the aggregometer and note the (positive) direction of recorder pen motion. Replace the cuvette. Using the

recorder zero knob, move the recorder pen in the positive direction to the chart paper 95% line. The pens now should not move when the red "zero" button is pressed. The pen also should not move when the mV sensitivity range is changed to 20 or 10 mV full scale (leave at 10 mV).

PMN aggregation should cause the pen to move in the "negative" direction across the chart paper. Make comparable adjustments for the second aggregometer channel but zero the recorder pen on the opposite side of the chart paper. Finally, pressing the zero button on either the recorder or the aggregometer should not cause the pens to move more than a mm or two. This instrument configuration will result in maximal pen deflection following aggregation of cells.

Aggregation studies

To a cuvette containing 334 ml of buffer and a flea magnet, add 166 ml of PMNs, 10 m of Ca^{++}/Mg^{++} (70/et mM; 1.4/0.7 mM final) and 5 ml of 10 mM cytochalasin-B allow to warm up in the aggregometer (37°C) for 5 minutes and then add 1 ml of test compound in DMSO or DMSO carrier alone. Note compound effects, if any, for 2 minutes, then add 5 ml of the challenge agonist (LTB_4, PAF, etc.) and observe the response for at least 2 minutes. The standard concentrations of agonists used in this assay are arachidonic acid, 6 mM; LTB_4, 0.3 nM; PAF, 30 pM; and FMLP, 0.6 nM.

Aggregation is quantitated by measuring, in millimeters, the average maximum deflection of the pen line at 1 minute or less after the addition of LTB_4. The maximum response to a control challenge with arachidonic acid may develop somewhat more slowly than this.

Each aggregometer-recorder channel should include its own series of control aggregations. All compounds should be tested at least twice at each concentration of interest. The inhibitory activity observed is expressed as the mean percent change (inhibition) observed relative to the controls determined in that channel. Controls must include appropriate solvent blanks.

The results of the above test demonstrate that compounds within the scope of this invention inhibit the activity of LTB_4.

The present invention also relates to pharmaceutical compositions comprising a product of general formula I, or its salt, optionally combined with any other compatible product, which may be inert or physiologically active. The compounds of the present invention can be administered in composition form to a mammalian host in a variety of forms adapted to the chosen route of administration, i.e., parenteral, oral, rectal or topical. Parenteral administration in this respect includes administration by the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepthelially including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, ocular and nasal inhalation via insufflation and aerosol and rectal includes systemic.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, trochees, capsules, elixirs, suspensions, syrups, wafers, and the like. By way of solid compositions for oral administration, tablets, pills, powders or granules may be used. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 6% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 50 and 300 mg of active compound.

The tablets, trochees, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be

present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens a preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

Compositions for parenteral administration may be aqueous or non-aqueous sterile solutions, suspensions or emulsions. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. By way of solvent or medium, propylene glycol, polyethylene glycol, vegetable oils, in particular olive oil, and injectable organic esters, for example ethyl oleate may be used. These compositions may also contain adjuvants, in particular wetting, emulsifying or dispersing agents.Dispersion can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. Sterilization may be performed in several ways, for example by means of a bacteriological filter, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions to be dissolved at the time of use in sterile water or any other injectable sterile medium.

Compositions for rectal administration are suppositories or rectal capsules which may contain, in addition to the active product, excipients such as cacao butter or Suppocire. Compositions for topical administration may be for example creams, pomades or lotions.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It may be stable under the conditions of manufacture and storage and must be

preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

In human therapy, the products according to the invention may be particularly useful in the treatment of diseases of inflammatory origin. They may therefore prove very useful in osteoarticulatory pathology in the treatment of arthritis, rheumatoid polyarthritis, spondylarthritis, gout, arthrosis, chondrocalcinosis, as well as in other inflammatory pathologies affecting the lungs, the digestive tracts (ulcerous colitis, hepatic inflammation, cirrhosis, diseases of the colon, Crohn's disease), the skin (psoriasis, herpes, acne, erythema, eczema, dermatitis), the eyes, the nasal tracts, the buccal cavity and the teeth. They may also be used in the treatment of nasal and bronchial allergies (asthma). The products according to the invention may also be useful in the treatment of inflammations connected with the fitting of implants, by improving their compatibility with the surrounding tissue. They may also play a

role in immuno-regulation (auto-immune diseases), ischemia and reperfusion (cardiac in particular). These products may also exert a beneficial effect in the treatment of hyperthermia and pain.

The physician will determine the dosage of the present therapeutic agents which will be most suitable for prophylaxis or treatment and it will vary with the form of administration and the particular compound chosen, and also, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages by small increments until the optimum effect under the circumstances is reached. The therapeutic dosage will generally be from 0.1 to 100 M/day or from about 0.1 mg to about 50 mg/kg of body weight per day and higher although it may be administered in several different dosage units. Higher dosages are required for oral administration. Generally, the physician will determine the dose he judges most suitable depending on the age, the weight and the other factors specific to the individual under treatment.

The therapeutic compounds of this invention may be administered to a mammal alone or in combination with pharmaceutically acceptable carriers, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice.

The following examples illustrate the compositions according to the invention.

EXAMPLE A

Tablets of the active product having the following composition are prepared according to the usual technique:

2,2-Dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy] hexanoic acid	100 mg
starch	332 mg
silica	120 mg
magnesium stearate	12 mg

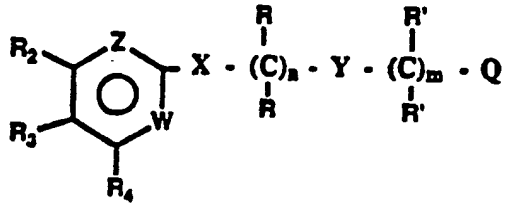
EXAMPLE B

Tablets of the active product having the following composition are prepared according to the usual technique:

5-{2,2-Dimethyl-5-[(4,6-diphenyl-2-pyridyl)-oxy]pentyl}-[1H]-tetrazole.....	100 mg
starch	332 mg
silica	120 mg
magnesium stearate	12 mg

CLAIMS

1. A compound of the formula:

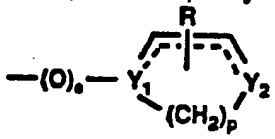


where

m is 1-8, n is 0-8 and n+m is 2-8;

X is S, O, NR", CR'R', CR'=CR', CO-NR", NR"-CO, CHR'-O or a bond;

Y is S, O, NR", CR'R', CR'=CR', CO-NR", NR"-CO, CO, CR'-OH, phenylene, naphthylene or a nitrogen-containing cyclene group of the formula

 where Y_1 and Y_2 are independently CR' or N, e is 0 or 1 and is 0 when Y_1 is N and p is 1-3;

W and Z are independently CR' or N provided that when both W and Z are N then n+m is 2-6;

R and R' are independently R_1 or R_1-loweralkyl- or vicinal R and/or R' groups together or vicinal R' and R" groups together may be $-(CH_2)_y-$ where y is 2-4, thus forming a 4-6 membered ring and geminal R and/or R' groups may together form a spiro substituent, $-CH_2-(CH_2)_z-CH_2-$ where z is 0-4 or an alkylidenyl substituent, $=CHR_5$, where R_5 is hydrogen or alkyl;

R" also may be hydrogen, alkyl or aralkyl;

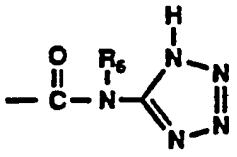
R_1 is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, aryl, hydroxy, alkoxy, aryloxy, aralkoxy, acyl, halo, amino, mono- and dialkylamino, aralkylamino, acylamino, carboxy, carbalkoxy, carbamyl or mono- and dialkylcarbamyl;

R_2, R_3 and R_4 are independently R_1, R_1-loweralkyl- or an optionally substituted mono- or bicyclic aryl or heteroaryl group containing about 5 to about 12 atoms wherein each ring comprising said group contains 0-2 hetero atoms selected from N, O or S provided said hetero atoms are not vicinal oxygen and/or sulfur atoms, and provided further that at least one of R_2, R_3 and R_4 is said aryl or heteroaryl group;

or, R_2, and R_3 or R_3 and R_4 together with the ring to which they are attached may form an optionally substituted fused bicyclic [5,6], [6,6] or [7,6] ring system which may contain from 0-2 hetero atoms in each ring selected from N, O and S, provided said hetero atoms are not vicinal oxygen and/or sulfur atoms;

R_4 also may be X_1-$(CH_2)_t$-R_3 provided that R_3 is said mono- or bicyclic aryl ring system, X_1 is S, O, NR", CR'R' or CO and t is 1-4; and

Q is $COOR_6$, COOM, $CONR_7R_7$, CN, $CONHSO_2R_6$, tetrazolyl or tetrazolyl substituted with alkyl, carboxyalkyl or carbalkoxyalkyl and



, where R_6 is hydrogen, alkyl or aralkyl, R_7 is hydrogen, alkyl, aralkyl or cycloalkyl, M is a metal or ammonia salt, and R_7 and R_7 together form a 3-6 membered ring provided that R_7 is hydrogen when R_2 and R_3 together or R_3 and R_4 together form a fused ring and n+m<5;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 where

m is 1 and n is 1-7;

X is S or O;

Y is O or CH_2;

Z is N and W is CR';

R and R' are independently hydrogen or alkyl;

R_2 and R_4 are independently hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, trifluoromethyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group;

R_3 is hydrogen or together with R_2 may form a fused benzene ring which may further be substituted with halo, alkyl or alkoxy; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

3. A compound according to claim 1 where

m is 2-7 and n is 0;

X is a bond;

Y is S or O;

W and Z are N;

R is hydrogen;

R' is independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2 and where R_1 is hydrogen, alkyl, aralkyl, aryl or halo;

R_2, R_3 and R_4 are independently hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, methylenedioxy, ethylenedioxy, aminomethyleneoxy, aminovinylene, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, ureodo,

trifluoroacetamido or benzamido or an aryl group selected from imidazol, thiazol or pyridyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2, R_3 and R_4 is said aryl group; or

R_3 together with R_2 may form a fused benzene ring which may further be substituted with halo, alkyl or alkoxy; and

Q is $COOR_6$, COONa, $CONR_7R_7$ or tetrazolyl where R_6 is hydrogen or alkyl.and R_7 is hydrogen or when R_3 together with R_2 may form a fused benzene ring may be alkyl when $n+m<5$.

4. A compound according to claim 1

where

m is 2-8 and n is 0

X is a bond;

Y is S or O;

Z is N and W is CR';

R is hydrogen;

R' is independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2 and where R_1 is hydrogen, alkyl, aralkyl, aryl or halo;

R_2, R_3 and R_4 are independently hydrogen, alkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, methylenedioxy, ethylenedioxy, aminomethyleneoxy, aminovinylene, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, ureodo, trifluoroacetamido or benzamido or an aryl group selected from imidazol, thiazol or pyridyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido,

trifluoroacetamido or benzamido provided at least one R_2, R_3, and R_4 is said aryl group and more than one said aryl groups are ortho to each other; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

5. A compound according to claim 1 where

m is 2-8 and n is 0;

X is S or O;

Y is a bond;

Z is N and W is CR';

R is hydrogen;

R' is independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2 and R_1 is hydrogen, alkyl, cycloalkyl, aralkyl, aryl or halo;

R_2, R_3 and R_4 are independently hydrogen, R' or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2, R_3 and R_4 is said aryl group; and

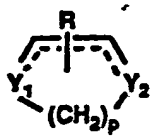
Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

6. A compound according to claim 1 where

n is 0-4, m is 0-5 and n+m 0-6;

X is S, O, CR'=CR' or CHR'-O;

Y is phenyl or a heterocyclic ring of the formula



where Y_1 and Y_2 are independently CR' or N and p is 1-3;

Z is N and W is CR';

R and R' are independently hydrogen or $(CH_2)_x$-R_1, where x is 0-2;

R_1 is hydrogen, alkyl, aralkyl, aryl or halo;

R_2, is hydrogen, alkyl, cycloalkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;

R_3 is hydrogen;

R_4, is hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido; provided at least one of R_2, and R_4 is said aryl group; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

7. A compound according to claim 1 where

m is 1-4 and n is 1-5;

X is S or O;

Y is CO-NR", NR"-CO, CO or CR'OH;

Z is N and W is CR';

R is hydrogen;

R' is independently hydrogen, or $(CH_2)_x$-R_1, where x is 0-2;

R" is hydrogen, alkyl or aralkyl;

R_1 is hydrogen, alkyl, aralkyl, aryl or halo;

R_2, is hydrogen, alkyl,cycloalkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;

R_3 is hydrogen;

R_4 is hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

8. A compound according to claim 1 where

m+n=2-8;

X is S, O, CR'R' or CR'=CR';

Y is CR'R';

Z and W are CR';

R is independently hydrogen or alkyl;

R' is independently hydrogen, alkyl, aralkyl, aryl or halo;

R_2, is hydrogen, alkyl,cycloalkyl or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;

R_3 is hydrogen or alkyl;

R_2 and R_3 together may form a fused benzene ring which may be substituted with a substituted or unsubstituted R_1 mono- or bicyclic aryl ring and/or further substituted with halo, alkyl, alkoxy or aralkoxy;

R_4 is hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 is hydrogen or alkyl.and R_7 is hydrogen or when R_2 and R_3 together may form a fused benzene ring may be alkyl when $m+n<5$.

9. A compound according to claim 1
where

$m+n=2-7$;

X is S, O, CR'R' or CR'=CR';

Y is CR'R';

Z is N or CR' and W is CR';

R is hydrogen;

R' is independently hydrogen, alkyl, aralkyl, aryl or halo;

R" is hydrogen or alkyl;

R_2 hydrogen, alkyl, cycloalkyl halo or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido;

R_3 hydrogen or an aryl group selected from phenyl, thienyl or furyl which may be substituted with 1-2 substituents independently selected from alkyl, alkoxy, methylenedioxy, halo, haloalkyl, alkylthio, nitro, amino, mono- and dialkylamino, acetamido, trifluoroacetamido or benzamido provided at least one of R_2 and R_4 is said aryl group;

R_4 is X_1-$(CH_2)_q$-R_3 where X_1 is O, NR", CR'R' or CO and q is 1-4; and

Q is $COOR_6$, COONa, $CONR_7R_7$, or tetrazolyl where R_6 and R_7 are independently hydrogen or alkyl.

10. A compound according to claim 1 where at least one of R_2, R_3 and R_4 is a substituted or unsubstituted mono- or bicyclic aryl or heteroaryl group or R_2 and R_3 together or R_3 and R_4 together are a fused ring and may be optionally substituted and where said substitution is independently selected from alkyl, alkoxy, hydroxy, acetoxy, benzoyloxy, methylenedioxy, ethylenedioxy, aminomethyleneoxy, aminovinylene, halo, haloalkyl, thio, alkylthio, nitro, amino, mono- and dialkylamino, cycloalkylamino, acetamido, ureido, trifluoroacetamido, benzamido, carboxy, carbalkoxy, carbaralkoxy, carbamyl, mono- and dialkylcarbamyl or arylcarbamyl.

11. A compound according to claim 1, which is2,2-dimethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid. or a pharmaceutically acceptable salt thereof.

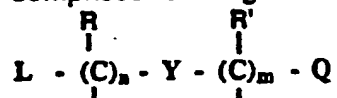
12. A compound according to claim 1, which is 2-ethyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid or a pharmaceutically acceptable salt thereof..

13. A compound according to claim 1, which is 2-Ethyl-2-methyl-6-[(4,6-diphenyl-2-pyridyl)oxy]hexanoic acid or a pharmaceutically acceptable salt thereof.

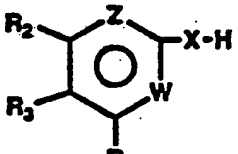
14. A compound according to claim 1, which is 2-Methyl-6-[[4-(3,4-methylenedioxyphenyl)-6-phenyl-2-pyridyl]oxy}-hexanoic acid or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 1, which is 5-[1,1-Dimethyl-5-[(4,6-diphenyl-2-pyridyl)oxy]pentyl]-[1H]-tetrazole or a pharmaceutically acceptable salt thereof.

16. A process for preparing a compound according to claim 1, which comprises reacting in basic medium a compound of the formula

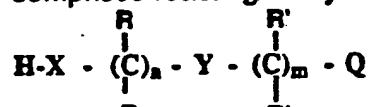


where Q is a nitrile, an ester or a tetrazolyl and L is a

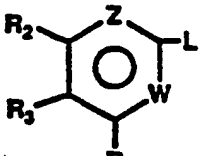


leaving group, with a compound of the formula , and when it is desired to prepare a compound for which Q is a carboxy radical, the ester obtained is converted to an acid and/or the product obtained is converted to a salt where necessary.

17. A process for preparing a compound according to claim 1, which comprises reacting an hydroxy, thiol or amino compound of the formula

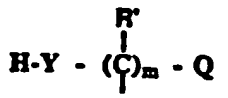


where Q is a nitrile, an ester or a tetrazolyl, with a

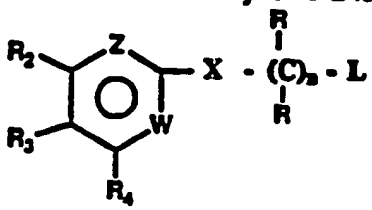


compound of the formula where L is a leaving group, and when it is desired to prepare a compound for which Q is a carboxy radical, the ester obtained is converted to an acid and/or the product obtained is converted to a salt where necessary.

18. A process for preparing a compound according to claim 1, which comprises reacting in basic medium a compound of the formula

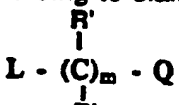


where Q is a nitrile, an ester or a tetrazolyl and L is a leaving group, with a compound of the formula

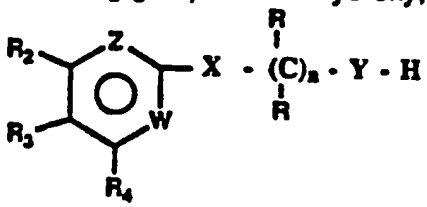


, and when it is desired to prepare a compound for which Q is a carboxy radical, the ester obtained is converted to an acid and/or the product obtained is converted to a salt where necessary.

19. A process for preparing a compound according to claim 1, which comprises reacting a compound of the formula

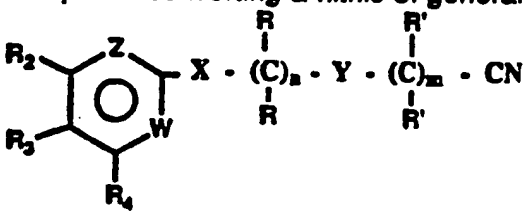


where Q is a nitrile, an ester or a tetrazolyl and L is a leaving group with an hydroxy, a thiol



or an amino compound of the formula , and when it is desired to prepare a compound for which Q is a carboxy radical, the ester obtained is converted to an acid and/or the product obtained is converted to a salt where necessary.

20. A process for preparing a compound according to claim 1, which comprises converting a nitrile of general formula



by any known method for converting a nitrile to an acid, an amide or a 5-tetrazolyl radical without affecting the rest of the molecule.

21. A process for preparing a compound according to claim 1 for which R_2 and/or R_4 contain an amino substituent, which comprises converting a product

according to claim 1 for which the said radical contains a nitro substituent, by any known method for reducing a nitro radical to an amino radical, without affecting the rest of the molecule, and then optionally converting the product obtained to a salt.

22. A process for preparing a compound according to claim 1 for which R_2 and/or R_4 contain an alkylamino or a dialkylamino substituent, which comprises converting a product according to claim 1 for which said radical contains an amino substituent, by any known method for alkylating an amino radical, without affecting the rest of the molecule and then converting where necessary the product obtained to a salt.

23. A process for preparing a compound according to claim 1 for which R_1 and/or R_2 contain a benzoylamino or trifluoro-acetamido substituent, which comprises converting a product according to claim 1 for which said radical contains an amino substituent, by any known method for acylating an amino radical, without affecting the rest of the molecule.

24. A pharmaceutical composition which contains at least one compound according to claim 1, in combination with a pharmaceutically acceptable diluent or adjuvant.

25. A method for the treatment of hypersensitive ailments in humans and mammals comprising administering thereto an effective amount of a compound of the formula according to Claim 1.

26. A method for the treatment of inflammatory diseases in humans and mammals comprising administering thereto an effective amount of a compound of the formula according to Claim 1.

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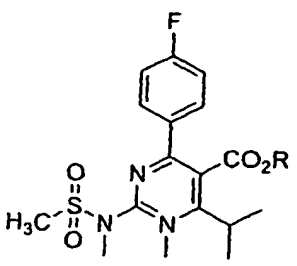
(54) Title: PREPARATION OF AMINOPYRIMIDINE COMPOUNDS



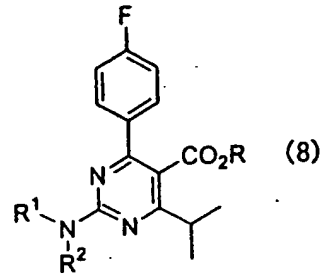
(3)

(57) Abstract: A 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound of the formula (3): [R is a hydrocarbyl group], is prepared by the steps of: (I) reacting an isobutyrylacetate ester with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt; (II) oxidizing the reaction product of the step (I); (III) reacting the oxidation product of the step (II) with an organic sulfonyl halide or an organic sulfonyl anhydride; and (IV) reacting the reaction product of the step (III) with N-methyl-N-methanesulfonamide.

PREPARATION OF AMINOPYRIMIDINE COMPOUNDS

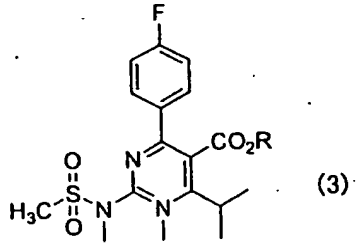
FIELD OF THE INVENTION

The present invention relates to the preparation of aminopyrimidine compounds having the following formula (8):



(8)

[in the formula (8), R is a hydrocarbyl group, and each of R^1 and R^2 independently is a hydrogen atom, an alkyl group, an alkylsulfonyl group, or an arylsulfonyl group], more particularly to the preparation of a 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound having the following formula (3):

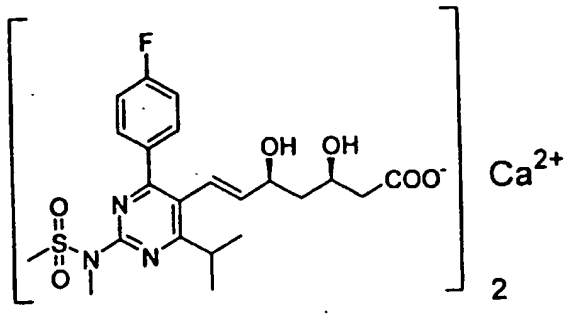


(3)

wherein R represents a hydrocarbyl group.

BACKGROUND OF THE INVENTION

Bioorg. Med. Chem., 5, 437(1997) describes that the 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound is employable as an intermediate compound for producing a cholesterol reducing agent (HMG-CoA reductase inhibitor: S-4522) having the following formula:



and which is now generally known as the calcium salt of rosuvastatin or rosuvastatin calcium.

WO 01/04100 describes a process for preparing the 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound which comprises the steps of:

reacting methyl isobutyrylacetate with 4-fluorobenzonitrile to produce methyl 2-[1-amino-1-(4-fluorophenyl)methylene]-4-methyl-3-oxopentanate; and

reacting the 2-[1-amino-1-(4-fluorophenyl)methylene]-4-methyl-3-oxopentanate with N-cyano-N-methylmethanesulfonamide which is obtained by reaction between N-methylmethanesulfonamide and cyanogen chloride, to produce 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methanesulfonyl-N-methylamino)pyrimidine.

It is described that the total yield (based on the amount of methyl isobutyrylacetate) is 45.5%.

It appears that the process described in WO 01/04100 is disadvantageous for the industrial preparation, because the yield is not high and it is necessary to employ toxic cyanogen chloride as one of the starting compounds.

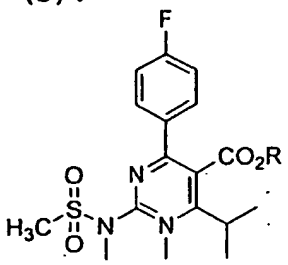
Accordingly, it is an object of the invention to provide a novel process for preparing a 2-(N-methyl-N-methanesulfonylamino)pyrimidine or an analogous aminopyrimidine compound thereof, more particularly to provide a novel process which provides the compound more conveniently and/or without employing a toxic compound and/or provides the compound in high yield and/or high purity.

It is another object of the invention to provide a

novel process for preparing a 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound or an analogous aminopyrimidine compound thereof which is favorably employable in the industrial preparation.

SUMMARY OF THE INVENTION

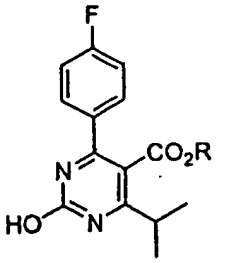
The present invention resides in a process for preparing a 2-(N-methyl-N-methanesulfonylamino)pyrimidine having the formula (3):



(3)

[R is a hydrocarbyl group],
which comprises the steps of:

reacting a hydroxypyrimidine compound having the formula (1):



(1)

in which R is the same as above,
with an organic sulfonyl halide having the formula (2):

$$R'SO_2X \qquad (2)$$

in which R' is a hydrocarbyl group and X is a halogen atom, or an organic sulfonic anhydride having the formula (2a):

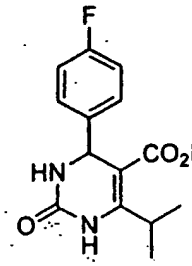
$(R'SO_2)_2O$ (2a)

in which R' is the same as above, and

reacting the resulting reaction product with N-methyl-N-methanesulfonamide.

The invention also resides in a hydroxypyrimidine compound having the above-identified formula (1).

The invention further resides in a method for preparing a hydroxypyrimidine compound of the formula (1), which comprises oxidizing a dihydropyrimidinone compound having the formula (4):

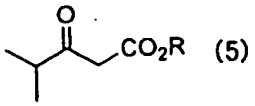


(4)

wherein R is a hydrocarbyl group.

The invention further resides in a dihydropyrimidinone compound having the formula (4).

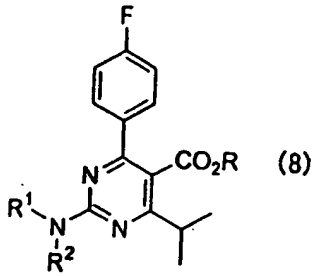
The invention furthermore resides in a method for preparing a dihydropyrimidinone compound of the formula (4), which comprises reacting an isobutyrylacetate ester having the formula (5):



(5)

in which R is a hydrocarbyl group,
with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt.

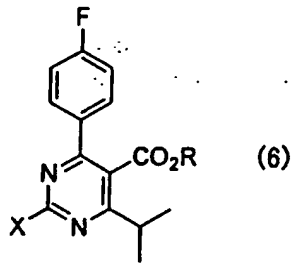
The invention furthermore resides in a method for preparing an aminopyrimidine compound having the formula (8):



(8)

wherein R is a hydrocarbyl group, and each of R^1 and R^2 independently is hydrogen atom, an alkyl group, an alkylsulfonyl group, or an arylsulfonyl group,

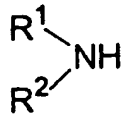
which comprises reacting a 2-substituted pyrimidine compound having the formula (6):



(6)

wherein R is the same as above, and X is a halogen atom or an organic sulfonyloxy group,

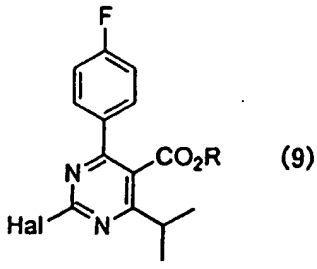
with an amine compound having the formula (7):



(7)

wherein each of R^1 and R^2 is the same as above.

The invention furthermore resides in a halogenopyrimidine compound having the formula (9):

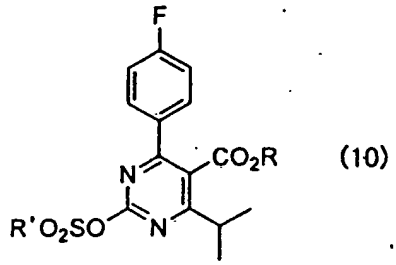


(9)

wherein R is a hydrocarbyl group, and Hal is a halogen atom.

The invention furthermore resides in a method for preparing the halogenopyrimidine compound of the formula (9), which comprises reacting a hydroxypyrimidine compound of the aforementioned formula (1) with a halogenating agent.

The invention furthermore resides in an organic sulfonyloxypyrimidine compound having the formula (10):



(10)

wherein each of R and R' independently is a hydrocarbyl group.

The invention furthermore resides in a method for preparing an organic sulfonyloxypyrimidine compound of the formula (10), which comprises reacting a hydroxypyrimidine compound of the aforementioned formula (1) with an organic sulfonyl halide having the formula (2):

$$R'SO_2X \qquad (2)$$

wherein R' is a hydrocarbyl group, and X is a halogen atom, or an organic sulfonic anhydride having the formula (2a):

$$(R'SO_2)_2O \qquad (2a)$$

in which R' is the same as above.

The invention furthermore resides in a process for preparing a 2-(N-methyl-N-methanesulfonylamino)pyrimidine of the formula (3) which comprises the steps of:

(I) reacting an isobutyrylacetate ester of the formula (5) with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt;

(II) oxidizing the reaction product of the step (I);

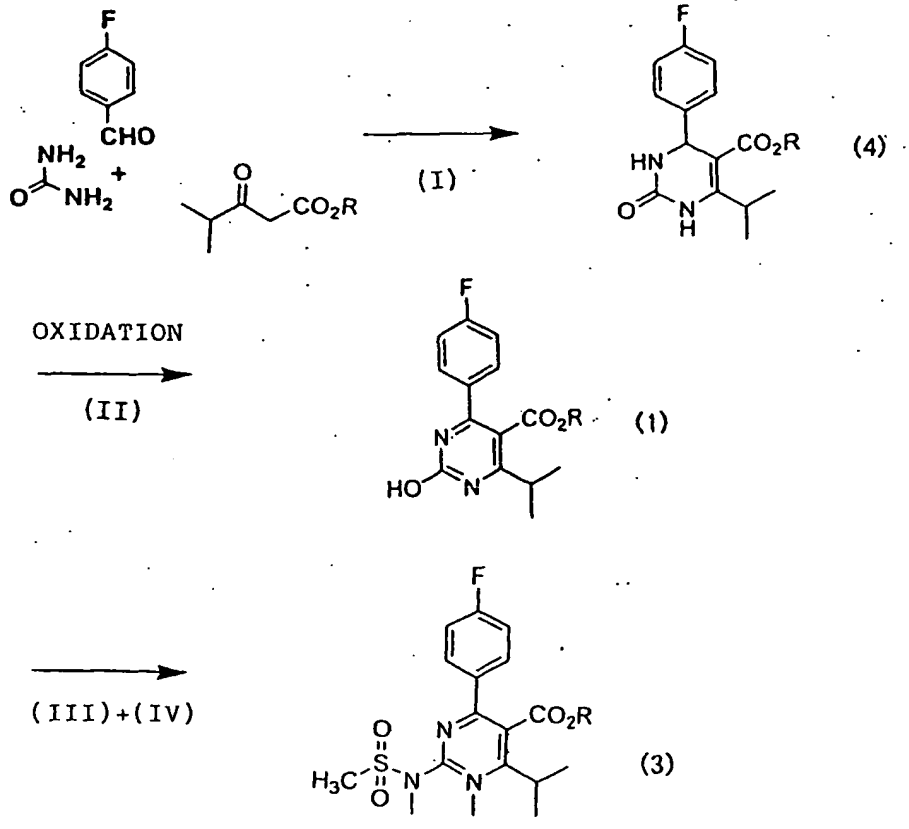
(III) reacting the oxidation product of the step (II) with an organic sulfonyl halide of the formula (2) or an organic sulfonic anhydride of the formula (2a); and

(IV) reacting the reaction product of the step (III) with N-methyl-N-methanesulfonamide.

In the above-mentioned process, the steps (III) and (IV) can be carried out continuously in the same reaction mixture.

DETAILED DESCRIPTION OF THE INVENTION

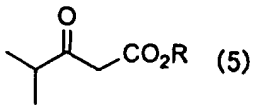
The representative process for the preparation of 2-(N-methyl-N-methanesulfonylamino)pyrimidine of the formula (3) according to the present invention is schematically illustrated as follows:



Each step in the above-illustrated reaction scheme is described below in more detail.

Step (I)

In the step (I), an isobutyrylacetate ester of the following formula (5):



(5)

[R is a hydrocarbyl group].

is reacted with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt.

The hydrocarbyl group (i.e., hydrocarbon group) represented by R in the formulas of the compounds involved in the reactions of the invention can be an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, or decyl, more particularly an alkyl group having 1-6 carbon atoms and especially an alkyl group having 1-4 carbon atoms; a cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; an aralkyl group such as benzyl, phenylethyl, or phenylpropyl; or an aryl group such as phenyl or methylphenyl. The hydrocarbyl group can take any isomer configurations such as normal, iso, and tertiary. The hydrocarbyl group can have one or more substituents, provided that the substituents do not disturb the reaction involved.

The protonic compound can be an inorganic acid or its salt such as hydrochloric acid, sulfuric acid, potassium hydrogensulfate, sodium hydrogen sulfate, nitric acid, or phosphoric acid; an organic sulfonic acid such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, or p-bromobenzenesulfonic acid; an organic carboxylic acid such as acetic acid, propionic acid, butyric acid, or benzoic acid; an

alcohol such as methanol, ethanol, or propanol. Preferred are protonic acids such as hydrochloric acid, sulfuric acid, p-toluenesulfonic acid, and acetic acid. Most preferred is sulfuric acid. The protonic compounds can be employed singly or in combination.

The protonic compound can be employed in an amount of, preferably, 0.01 to 3 mol., more preferably 0.1 to 1 mol., per one mol. of the isobutyrylacetate ester.

The metal salt employed in the reaction can be copper(I) chloride, copper(II) chloride, copper(II) acetate, iron(II) chloride, iron(III) chloride, aluminum chloride, nickel(II) bromide, tin(IV) chloride, titanium tetrachloride, or magnesium bromide. Preferred are copper(I) chloride, copper(II) chloride, iron(III) chloride and nickel(II) bromide. Most preferred is copper(I) chloride. The metal salts may contain water of crystallization. The metal salts can be employed singly or in combination.

The metal salt can be employed in an amount of, preferably, 0.001 to 5 mol., more preferably 0.01 to 0.1 mol., per one mol. of the isobutyrylacetate ester.

The 4-fluorobenzaldehyde can be employed in an amount of, preferably, 0.5 to 10 mol., more preferably 0.9 to 1.1 mol., per one mol. of the isobutyrylacetate ester.

The urea can be employed in an amount of, preferably, 0.5 to 10 mol., more preferably 1.5 to 2 mol., per one mol. of the isobutyrylacetate ester.

The reaction can be performed in the presence or absence of a solvent. There are no specific limitations with respect to the solvent employed, so far as the solvent does not disturb the desired reaction. Examples of the employable solvents include alcohols such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, isobutyl alcohol, sec-butyl alcohol, and t-butyl alcohol; ethers such as diethyl ether, diisopro-

pyl ether, tetrahydrofuran, and dimethoxyethane; nitriles such as acetonitrile, propionitrile, butyronitrile, and isobutyronitrile; halogenated aliphatic hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated aromatic hydrocarbons such as chlorobenzene; and nitrated aromatic hydrocarbons such as nitrobenzene. Preferred are methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, diisopropyl ether, tetrahydrofuran, dimethoxyethane, acetonitrile, butyronitrile, isobutylonitrile, dichloromethane, dichloroethane, chloroform, toluene, xylene, and chlorobenzene. Especially preferred are methanol, ethanol, and isopropyl alcohol. The solvents can be employed singly or in combination.

The solvent can be employed in an amount of, preferably 0.1 to 10 liters, more preferably 0.3 to 2 liters, per one mole of the isobutyrylacetate ester. The amount may vary depending on homogeneity and dispersability of the reaction mixture.

The reaction can be conducted by reacting the isobutyrylacetate ester, 4-fluorobenzaldehyde, and urea, in a solvent in the presence of a protonic compound and a metal salt under inert gas atmosphere. The reaction can be carried out at a temperature of, preferably -10 to 200°C, more preferably 30 to 100°C. There are no specific limitations with respect to the surrounding pressure.

The resulting product of the reaction, that is, a dihydropyrimidinone compound of the formula (4), can be isolated and purified according to the conventional procedures such as distillation, crystallization, recrystallization, and column chromatography.

Step (II)

In the step (II), a dihydropyrimidinone compound of the formula (4), that is, the reaction product of the

step (I), is oxidized to give a hydroxypyrimidine compound of the formula (1).

The oxidation (or dehydrogenation oxidation) can be performed in various conventional manners. Preferred is oxidation utilizing nitric acid, because this oxidation procedure is easily carried out and the post-treatment of the reaction product is easy.

The nitric acid can be employed in an amount of, preferably 1 to 20 mol., more preferably 3 to 15 mol., per one mole of the dihydropyrimidinone compound of the formula (4). The nitric acid of a concentration of, preferably 40 to 80%, more preferably 50 to 70%, can be preferably employed.

The oxidation can be performed in the presence or absence of a solvent. There are no specific limitations with respect to the solvent employed, so far as the solvent does not disturb the desired reaction. Examples of the preferred solvents include carboxylic acids such as acetic acid, propionic acid, and butyric acid. The solvents can be employed singly or in combination.

The solvent can be employed in an amount of, preferably 0.1 to 7 mL, more preferably 0.5 to 3 mL, per 1 g of the dihydropyrimidinone compound. The amount may vary depending on homogeneity and dispersability of the reaction mixture.

The oxidation can be conducted by reacting the dihydropyrimidinone compound and nitric acid in a solvent under inert gas atmosphere. The oxidation can be carried out at a temperature of, preferably -10 to 100°C, more preferably 0 to 50°C. There are no specific limitations with respect to the surrounding pressure. A reaction initiator such as sodium nitrite may be incorporated into the reaction system to accelerate the oxidation rate.

The resulting product of the reaction, that is, the hydroxypyrimidine compound of the formula (1), can be isolated and purified according to the conventional pro-

cedures such as distillation, crystallization, recrystallization, and column chromatography.

Steps (III) and (IV)

In the steps (III) and (IV), a hydroxypyrimidine compound of the formula (1), that is, the reaction product of the step (II), is reacted with an organic sulfonyl halide of the formula (2):

$$R'SO_2X \qquad (2)$$

or an organic sulfonic anhydride of the formula (2a):

$$(R'SO_2)_2O \qquad (2a)$$

and

reacting the resulting reaction product with N-methyl-N-methanesulfonamide.

In the formulas (2) and (2a), R' is a hydrocarbyl group which can have one or more substituents. Examples of the hydrocarbyl groups include alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, heptyl, octyl, nonyl, and decyl, more particularly an alkyl group having 1-6 carbon atoms and especially an alkyl group having 1-4 carbon atoms; fluorinated alkyl groups such as trifluoromethyl, nonafluorobutyl, tridecafluorohexyl, heptadecafluorooctyl, and uncosafluorodecyl; cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; aralkyl groups such as benzyl, phenylethyl, and phenylpropyl; and aryl groups, including unsubstituted and substituted phenyl or naphthyl groups, such as phenyl, naphthyl, tolyl, xylyl, mesityl, triisopropylphenyl, methoxyphenyl, chlorophenyl, and nitrophenyl. Thus, the hydrocarbyl group can have one or more substituents, provided that the substituents do not disturb the reaction involved. The hydrocarbyl group can take any isomer con-

figurations such as normal, iso, and tertiary. A particularly suitable value for R' when it is aryl includes, for example, a phenyl or naphthyl group (particularly phenyl) which is unsubstituted or bears 1, 2 or 3 substituents. The substituents may be independently selected from, for example, alkyl having 1-4 carbon atoms, alkoxy having 1-4 carbon atoms, halogeno, and nitro.

In the formula (2), X is a halogen atom such as fluorine, chlorine, bromine, and iodine.

Examples of the sulfonyl halides include methanesulfonyl fluoride, methanesulfonyl chloride, ethanesulfonyl chloride, 1-propanesulfonyl chloride, 2-propanesulfonyl chloride, trifluoromethanesulfonyl fluoride, trifluoromethanesulfonyl chloride, nonafluorobutanesufonyl fluoride, tridecafluorohexanesulfonyl fluoride, heptadecafluorooctanesulfonyl fluoride, uncosafluorodecanesulfonyl fluoride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, p-toluenesulfonyl fluoride, p-toluenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2,4,6-triisopropylbenzenesulfonyl chloride, p-methoxybenzenesulfonyl chloride, p-chlorobenzenesulfonyl chloride, and 2-nitrobenzenesulfonyl chloride. Preferred are trifluoromethanesulfonyl fluoride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, p-toluenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2,4,6-triisopropylbenzenesulfonyl chloride, p-methoxybenzenesulfonyl chloride, and p-chlorobenzenesulfonyl chloride. Particularly preferred are p-toluenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2,4,6-triisopropylbenzenesulfonyl chloride, and p-methoxybenzenesulfonyl chloride.

Examples of the sulfonic anhydrides include methanesulfonic anhydride, trifluoromethanesulfonic anhydride, benzenesulfonic anhydride, and p-toluenesulfonic anhydride. Preferred are trifluoromethanesulfonic anhydride,

benzenesulfonic anhydride, and p-toluenesulfonic anhydride. Particularly preferred are trifluoromethanesulfonic anhydride and p-toluenesulfonic anhydride.

The sulfonyl halide or sulfonic anhydride can be employed in an amount of, preferably 0.1 to 20 mol., more preferably 0.5 to 5 mol., most preferably 1 to 2 mol., per one mole of the hydroxypyrimidine compound.

In the subsequent step, N-methylmethanesulfonamide can be employed in an amount of, preferably 0.1 to 30 mol., more preferably 1 to 5 mol., per one mol. of the hydroxypyrimidine compound.

The reactions of the steps (III) and (IV) can be preferably performed in the presence of a base. Examples of the bases include alkali metal carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrogencarbonates such as sodium hydrogencarbonate; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide; alkali metal alkoxides such as sodium methoxide, sodium t-butoxide, potassium t-butoxide, and sodium t-pentoxide; and tertiary amines such as triethylamine, triisopropylamine, diisopropylethylamine, and pyridine. Preferred are sodium carbonate, potassium carbonate, potassium t-butoxide, sodium t-pentoxide, triethylamine, and pyridine. Particularly preferred are potassium carbonate, sodium t-pentoxide, and triethylamine. Most preferred are potassium carbonate and sodium t-pentoxide. The bases can be employed singly or in combination.

The base can be employed in an amount of, preferably 0.1 to 30 mol., more preferably 1 to 5 mol., per one mol. of the hydroxypyrimidine compound. The whole amount of the base can be incorporated in the reaction system before the reaction begins, or the base can be portionwise added to the reaction system after the reaction begins.

The reaction can be performed in the presence or absence of a solvent. There are no specific limitations

with respect to the solvent, so far as the solvent does not disturb the reaction. Examples of the solvents include water; ketones such as acetone, methyl ethyl ketone, and diethyl ketone; ethers such as diethyl ether and tetrahydrofuran; esters such as ethyl acetate, propyl acetate, and butyl acetate; nitriles such as acetonitrile and propionitrile; amides such as N,N-dimethylformamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide; ureas such as N,N'-dimethylimidazolinone. Preferred are acetone, tetrahydrofuran, ethyl acetate, butyl acetate, acetonitrile, N,N-dimethylformamide, and dimethylsulfoxide. Particularly preferred are ethyl acetate, butyl acetate and acetonitrile. Most preferred are butyl acetate and acetonitrile. The solvents can be employed singly or in combination.

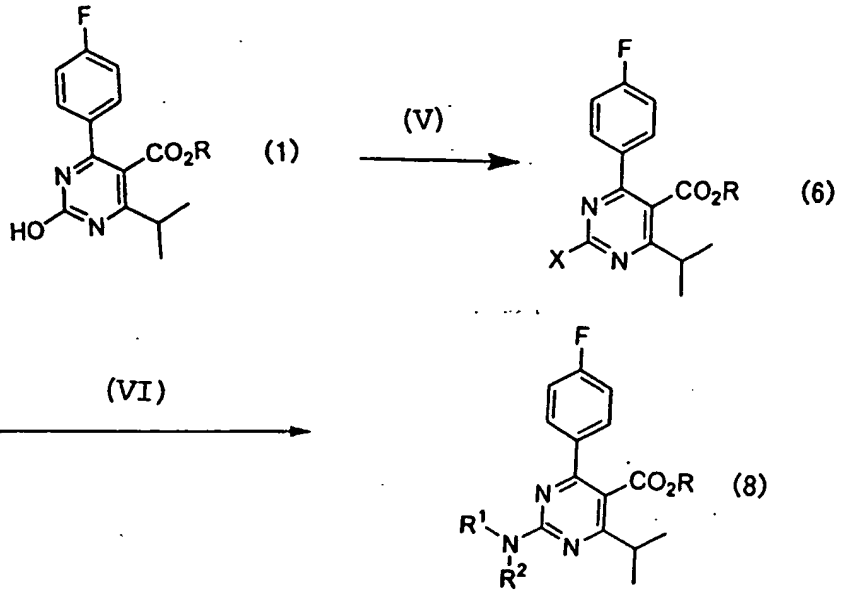
The solvent can be employed in an amount of, preferably 0.01 to 100 liters, more preferably 0.5 to 5 liters, per one mole of the hydroxypyrimidine compound. The amount may vary depending on homogeneity and dispersability of the reaction mixture.

The reaction can be performed by reacting the hydroxypyrimidine compound and the organic sulfonyl halide or sulfonic anhydride in a solvent in the presence of a base with stirring under inert gas atmosphere. The base can be added portionwise. The reaction can be carried out at a temperature of, preferably -30 to 250°C, more preferably 0 to 150°C. There are no specific limitations with respect to the surrounding pressure.

The resulting product of the reaction, that is, the 2-(N-methyl-N-methanecarbonsulfonylamino)pyrimidine compound of the formula (3), can be isolated and purified according to the conventional procedures such as distillation, crystallization, recrystallization, and column chromatography.

The 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound of the formula (3) and other pyrimidine com-

pounds of the formula (8) can be prepared from a hydroxypyrimidine compound of the formula (1) via a 2-substituted pyrimidine compound of the formula (6) in the following steps (V) and (VI):



In the formula (8), R has the same meaning as described above, and each of R^1 and R^2 independently is a hydrogen atom, an alkyl group, an alkylsulfonyl group, or arylsulfonyl group.

Step (V)

In the step (V), a hydroxypyrimidine compound of the formula (1) is reacted with a halogenating agent such as a chlorinating agent, an organic sulfonyl halide of the formula (2):

$$R'SO_2X \qquad (2)$$

in which R' has the same meaning as above and X is a halogen atom, or an organic sulfonic anhydride of the formula (2a):

$$(R'SO_2)_2O \qquad (2a)$$

in which R' has the same meaning as above.

Examples of the halogenating agents include phosphorus oxychloride and thionyl chloride. The halogenating agents can be employed singly or in combination.

The halogenating agent can be employed in an amount of, preferably 0.1 to 50 mol., more preferably 1 to 20 mol., most preferably 1.5 to 10 mol., per one mol. of the hydroxypyrimidine compound.

Examples of the organic sulfonyl halides and sulfonic anhydrides are those described hereinbefore.

The organic sulfonyl halide or sulfonic anhydride can be employed in an amount of, preferably 0.1 to 20 mol., more preferably 0.5 to 5 mol., most preferably 1 to 2 mol., per one mol. of the hydroxypyrimidine compound.

The reaction can be performed in the presence or absence of a solvent. There are no specific limitations with respect to the solvent, so far as the solvent does not disturb the reaction. Examples of the solvents include aromatic hydrocarbons such as toluene; halogenated aromatic hydrocarbons such as chlorobenzene; nitrated hydrocarbons such as nitrobenzene; halogenated aliphatic hydrocarbons such as methylene chloride and 1,2-dichloroethane; amides such as N,N-dimethylformamide; water (not for a halogenating agent); nitriles such as acetonitrile and propionitrile; carboxylic acid esters such as ethyl acetate, propyl acetate, butyl acetate; ketones such as acetone, methyl ethyl ketone, diethyl ketone; and ethers such as diethyl ether and tetrahydrofuran. Preferred are butyl acetate, toluene, methylene chloride, acetonitrile, chlorobenzene, nitrobenzene, and N,N-dimethylformamide. The solvents can be employed singly or in combination.

The solvent can be employed in the reaction utilizing the halogenating agent in an amount of, preferably 0.01 to 10 liters, more preferably 0.1 to 2 liters, per one mole of the hydroxypyrimidine compound. The amount may vary depending on homogeneity and dispersability of

the reaction mixture.

The solvent can be employed in the reaction utilizing the sulfonyl chloride or sulfonic anhydride in an amount of, preferably 0.1 to 50 liters, more preferably 0.5 to 2 liters, per one mole of the hydroxypyrimidine compound. The amount may vary depending on homogeneity and dispersability of the reaction mixture.

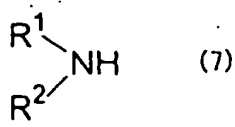
The reaction can be carried out by reacting the hydroxypyrimidine compound and the halogenating agent, in a solvent with stirring under inert gas atmosphere. The reaction can be carried out at a temperature of, preferably 0 to 200°C, more preferably 50 to 120°C. There are no specific limitations with respect to the surrounding pressure.

The reaction can be carried out by reacting the hydroxypyrimidine compound and the sulfonyl halide or sulfonyl anhydride in a solvent with stirring under inert gas atmosphere. The reaction can be carried out at a temperature of, preferably -30 to 200°C, more preferably 0 to 50°C. There are no specific limitations with respect to the surrounding pressure.

The resulting product of the reaction, that is, a 2-substituted pyrimidine compound such as a chloropyrimidine compound or a sulfonyloxypyrimidine compound, can be isolated and purified according to the conventional procedures such as distillation, crystallization, recrystallization, and column chromatography.

Step (VI)

In the step (VI), the 2-substituted pyrimidine compound, such as a chloropyrimidine compound or a sulfonyloxypyrimidine compound prepared in the step (V) is reacted with an amine compound having the formula (7):



(7)

wherein each of R^1 and R^2 is the same as above.

Examples of the groups of R^1 and R^2 include a hydrogen atom, alkyl groups such as methyl, ethyl, propyl, butyl, pentyl and hexyl; alkylsulfonyl groups such as methanesulfonyl; and arylsulfonyl groups such as benzenesulfonyl and p-toluenesulfonyl.

The amine compound can be employed in an amount of, preferably 0.1 to 30 mol., more preferably 1 to 5 mol., per one mol. of the 2-substituted pyrimidine compound.

The reaction is preferably performed in the presence of a base. Examples of the bases are those described hereinbefore.

The base can be preferably employed in an amount of, preferably 0.1 to 30 mol., more preferably 1 to 5 mol., per one mol. of the 2-substituted pyrimidine compound.

The reaction can be performed in the presence or absence of a solvent. There are no specific limitations with respect to the solvent, so far as the solvent does not disturb the reaction. Examples of the solvents include water; ketones such as acetone, methyl ethyl ketone, and diethyl ketone; ethers such as diethyl ether and tetrahydrofuran; esters such as ethyl acetate, propyl acetate, and butyl acetate; nitriles such as acetonitrile and propionitrile; amides such as N,N-dimethylformamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide; ureas such as N,N'-dimethylimidazolidinone. Preferred are acetone, tetrahydrofuran, ethyl acetate, butyl acetate, acetonitrile, N,N-dimethylformamide, and dimethylsulfoxide. Particularly preferred are ethyl acetate, butyl acetate and acetonitrile. The solvents can be employed singly or in combination.

The solvent can be employed in an amount of, preferably 0.01 to 100 liters, more preferably 0.5 to 5 liters, per one mole of the 2-substituted pyrimidine compound. The amount may vary depending on homogeneity and dispersability of the reaction mixture.

The reaction can be conducted by reacting the 2-substituted pyrimidine compound and the amine compound in a solvent in the presence of a base with stirring under inert gas atmosphere. The reaction can be carried out at a temperature of, preferably -20 to 250°C, more preferably 25 to 150°C. There are no specific limitations with respect to the surrounding pressure.

The reaction can be conducted in two separate liquid phases in the presence of a phase transfer catalyst. Examples of the phase transfer catalysts include tetramethylammonium chloride, tetramethylammonium bromide, tetraethylammonium fluoride, tetraethylammonium chloride, tetraethylammonium bromide, tetrapropylammonium bromide, tetrapropylammonium iodide, tetrabutylammonium fluoride, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, tetrapentylammonium bromide, tetrahexylammonium bromide, tetraheptylammonium bromide, tetraoctylammonium bromide, benzyldimethyltetradecylammonium chloride, benzyltriethylammonium chloride, phenyltrimethylammonium chloride, phenyltrimethylammonium iodide, and hexadecyltrimethylammonium chloride. Preferred are tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodided, benzyltriethylammonium chloride, and hexadecyltrimethylammonium chloride. Most preferred are tetrabutylammonium bromide, benzyltriethylanmonium chloride, and hexadecyltrimethylammonium chloride.

The phase transfer catalyst can be employed in an amount of 0.01 to 0.5 mol., preferably 0.05 to 0.2 mol., per one mol. of the 2-substituted pyrimidine compound.

The resulting product of the reaction, that is, a 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound of the formula (3) or other aminopyrimidine compounds of formula (8), can be isolated and purified according to the conventional procedures such as distillation, crystallization, recrystallization, or column chromatography.

The present invention is further described by the following non-limiting examples.

[Example 1] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone

In a 500 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 28.8 g (0.2 mol.) of methyl isobutyrylacetate, 24.8 g (0.2 mol.) of 4-fluorobenzaldehyde, 21.0 g (0.35 mol.) of urea, 200 mg (2 mmol.) of copper(I) chloride, 2 mL of sulfuric acid, and 200 mL of methanol. The content of the flask was heated to 64-65°C for 24 hours under reflux with stirring, to carry out the reaction. There was precipitated crystalline product. The crystalline product was collected on a filter paper and washed with methanol to obtain 49.7 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone as a colorless crystalline product having the below-mentioned characteristics. The yield was 85% (based on the amount of methyl isobutyrylacetate).

m.p.: 223-225°C

UV λ_{max} (CH_3CN, nm): 194.3, 278.6

IR (KBr, cm^{-1}): 3296, 3229, 3137, 2963, 1685, 1629, 1504, 1225, 1097.

^{1}H-NMR (DMSO-d_6, δ (ppm)): 1.14 (6H, dd, J=6.8, 6.9Hz), 3.52 (3H, s), 4.0-4.2 (1H, m), 5.15 (1H, d, J=3.4Hz), 7.1-7.2 (2H, m), 7.2-7.3 (2H, m), 7.76 (1H, d, J=3.2Hz), 8.91 (1H, s).

HRMS: 292.1247 (theoretical value ($C_{15}H_{17}FN_2O_3$(M+)) 292.1223)

[Example 2] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone

The procedures of Example 1 were repeated except for

replacing 200 mg (2 mmol.) of copper(I) chloride with 5.41 g (20 mmol.) of iron(III) chloride·hexahydrate. There was obtained 35.6 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone. The yield was 61% (based on the amount of methyl isobutyryl-acetate).

[Example 3] Preparation of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine

In a 50 mL-volume glass flask equipped with a stirrer and a thermometer was placed 11 mL (144 mmol.) of nitric acid (60-61%, sp.gr.: 1.38). To the nitric acid was slowly added at room temperature 4.00 g (13.7 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone prepared in the same manner as in Example 1, and the mixture was subjected to reaction for 30 minutes at room temperature. After the reaction was complete, the reaction mixture was neutralized by placing the mixture in 140 mL of saturated aqueous sodium hydrogen carbonate solution. The reaction mixture was then extracted with ethyl acetate. The organic liquid portion was separated and concentrated under reduced pressure. The residue was crystallized from toluene. The crystalline product was collected on a filter and washed with toluene to obtain 3.64 g of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonyl-pyrimidine as a colorless crystalline product having the below-mentioned characteristics. The yield was 92% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone).

m.p.: 193°C (decomposed)

UV λ_{max} (CH_3CN, nm): 196.6, 243.2, 317.9

IR (KBr, cm^{-1}): 2991, 2887, 1717, 1653, 1589, 1433, 1280, 1223.

^{1}H-NMR (DMSO-d_6, δ (ppm)): 1.23 (6H, d, J=6.8Hz),

3.0-3.2 (1H, m), 3.56 (3H, s), 7.3-7.4 (2H, m), 7.5-7.6 (2H, m), 12.25 (1H, brs).

HRMS: 290.1054 (theoretical value ($C_{15}H_{15}FN_2O_3$(M+)) 290.1067)

[Example 4] Preparation of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine

In a 50 mL-volume glass flask equipped with a stirrer and a thermometer were placed 2.92 g (10 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone prepared in the same manner as in Example 1 and 5 mL of acetic acid. To the mixture was slowly added 3.74 mL (50 mmol.) of nitric acid (60-61%, sp.gr.: 1.38). To the mixture was further added 0.07 g (1 mmol.) of sodium nitrite, and the reaction was carried out for one hour at room temperature. After the reaction was complete, the reaction mixture was neutralized by placing the mixture in 50 mL of saturated aqueous sodium hydrogen carbonate solution. The reaction mixture was then extracted with ethyl acetate. The organic liquid portion was separated and concentrated under reduced pressure. The residue was crystallized from toluene. The crystalline product was collected on a filter and washed with toluene to obtain 2.61 g of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonyl-pyrimidine as a colorless crystalline product. The yield was 90% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone).

[Example 5] Preparation of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine

In a 200 mL-volume glass flask equipped with a stirrer and a thermometer was placed 54.0 g (735 mmol.) of nitric acid (60-61%, sp.gr.: 1.38). To the nitric acid was slowly added at room temperature 30.6 g (105 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-

2(1H)-dihydropyrimidinone prepared in the same manner as in Example 1, and the mixture was subjected to reaction for 30 minutes at room temperature. After the reaction was complete, the reaction mixture was poured into 162 mL of water. The aqueous mixture was neutralized by adding 61 g of aqueous sodium hydroxide solution (48 wt.%) to precipitate a crystalline product. The crystalline product was collected by filtration and dried to obtain 27.6 g of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine as a colorless crystalline product. The yield was 91% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone).

[Example 6] Preparation of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine

In a 2 L-volume glass flask equipped with a stirrer and a thermometer was placed 323.3 g (3.09 mol.) of nitric acid (60-61%, sp.gr.: 1.38). The concentrated nitric acid was then cooled to 10°C. To the nitric acid was added 2.36 g (34.2 mmol.) of sodium nitrite, and was further added slowly 100 g (342 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone prepared in the same manner as in Example 1. The mixture was subjected to reaction for 2 hours at a temperature of 10-12°C. After the reaction was complete, 970 mL of water was poured into the reaction mixture. The aqueous mixture was then neutralized by adding 257 g of aqueous sodium hydroxide solution (48 wt.%) to precipitate a crystalline product. The crystalline product was collected by filtration and dried to obtain 93.3 g of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine as a colorless crystalline product. The yield was 94% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-

dihydropyrimidinone).

[Example 7] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine

In a 200 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 5.81 g (20 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine, 3.59 g (26 mmol.) of potassium carbonate (available from Asahi Glass Works, Co., Ltd., Lot No. 1111632, particle size distribution: 75-250 μm: 14%, 75 μm pass: 86%), and 40 mL of butyl acetate. To the mixture was slowly added 4.19 g (22 mmol.) of p-toluenesulfonyl chloride under stirring, and the reaction was carried out at 40°C for 4 hours. Subsequently, the reaction mixture was cooled to room temperature. To the cooled reaction mixture were added 2.84 g (26 mmol.) of N-methylmethanesulfonamide and 4.15 g (30 mmol.) of potassium carbonate (same as above). The mixture was heated to 110-125°C for 2 hours under refluxing to carry out a reaction. After the reaction was complete, the mixture was cooled to room temperature. To the cooled mixture were added 25 mL of water and 20 mL of acetone, and the organic liquid portion was separated. The organic liquid portion was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The dry organic liquid portion was filtered and concentrated under reduced pressure. The residue was crystallized from heptane, to obtain 6.58 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine as a pale yellow crystalline product. The yield was 86% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

[Example 8] Preparation of 4-(4-fluorophenyl)-6-isopro-

pyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonyl-amino)pyrimidine

In a 1000 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 50.0 g (172 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine, 20.8 g (189 mmol.) of sodium t-pentoxide, and 344 mL of acetonitrile, and the resulting mixture was stirred at 0-10°C for 30 minutes. To the mixture was slowly added 36.1 g (189 mmol.) of p-toluenesulfonyl chloride, and the reaction was carried out at for 5 hours at room temperature. Subsequently, the reaction mixture was cooled to a temperature of 0-10°C. To the cooled reaction mixture were added 28.2 g (258 mmol.) of N-methylmethanesulfonamide and 26.5 g (241 mmol.) of sodium t-pentoxide. The mixture was kept at 0-10°C for one hour and then heated to 75-82°C for 2 hours under refluxing, to carry out a reaction. After the reaction was complete, the mixture was cooled to room temperature. To the cooled mixture was added 344 mL of water. The aqueous mixture was cooled to 0-10°C and stirred for one hour, precipitating a crystalline product. The crystalline product was collected by filtration and dried, to obtain 45.3 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine as a pale yellow crystalline product. The yield was 68% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonyl-pyrimidine).

[Example 9] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonyl-amino)pyrimidine from methyl isobutyrylacetate, 4-fluorobenzaldehyde and urea

1) In a 200 L-volume glass-lined reaction vessel equipped with a stirrer, a thermometer and a reflux condenser were placed 24.4 kg (169 mol.) of methyl iso-

butyrylacetate, 20.0 kg (161 mol.) of 4-fluorobenzaldehyde, 16.9 kg (282 mol.) of urea, 0.2 kg (2 mol.) of copper(I) chloride, 3.0 kg of sulfuric acid, and 80.4 kg of methanol. The mixture was heated to 64-66°C for 20 hours under refluxing, to carry out reaction. After the reaction was complete, the reaction mixture was cooled to room temperature, to precipitate a crystalline product. The crystalline product was collected on a filter paper and washed with methanol to obtain 43.4 kg of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone as a colorless crystalline product.

2) In a 200 L-volume glass-lined reaction vessel equipped with a stirrer and a thermometer were placed 62.5 kg (615.6 mol.) of diluted nitric acid and 0.5 kg (6.8 mol.) of sodium nitrite. To the mixture was slowly added under chilling 20.0 kg (68.4 mmol.) of the 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-3,4-2(1H)-dihydropyrimidinone prepared as above. The resulting mixture was subjected to reaction at a low temperature (10°C). After the reaction was complete, the reaction mixture was neutralized by addition of an aqueous methanol solution of sodium hydroxide. Subsequently, an aqueous sodium hydroxide solution was added to the mixture. The resulting mixture was placed under reduced pressure to distill methanol off. To the residue were added 96.5 kg of acetone and 96.5 kg of water. The aqueous residue was then neutralized by addition of acetic acid to precipitate a crystalline product. The crystalline product was collected on a filter paper and washed with a acetone/water mixture, to give 17.9 kg of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine.

3) In a 200 L-volume glass-lined reaction vessel equipped with a stirrer, a thermometer and a reflux condenser were placed 17.9 kg (62.0 mol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine prepared as above, 107.7 kg of butyl acetate, 11.1 kg

(80.3 mol.) of potassium carbonate (available from Asahi Glass Works, Co., Ltd., Lot No. 1111632, particle size distribution: 75-250 μm: 14%, 75 μm pass: 86%), and 12.9 kg (67.7 mol.) of p-toluenesulfonyl chloride. The mixture was heated at 60°C for 2 hours, to carry out reaction. Subsequently, the reaction mixture was cooled to room temperature. To the cooled mixture were added 8.8 kg (80.6 mol.) of N-methylmethanesulfonamide and 12.9 kg (93.3 mol.) of potassium carbonate, and the resulting mixture was heated at 122-125°C for 3 hours, for carrying reaction. After the reaction was complete, the reaction mixture was cooled to room temperature. To the cooled mixture were added acetone and water, and the organic liquid portion was separated. The organic liquid portion was then washed successively with aqueous sodium hydroxide solution (3 wt.%) and a saturated aqueous sodium chloride solution. The washed organic liquid portion was concentrated under reduced pressure. Isopropyl alcohol and water were added to the residue, resulting in precipitation of a crystalline product. The crystalline product was filtered on a filter paper and washed with isopropyl alcohol. The washed crystalline product and 85.7 kg of acetone were placed in a 200 L-volume glass lined reaction vessel equipped with a stirrer, a thermometer and a reflux condenser. The mixture was stirred at 50-55°C, to dissolve the crystalline product in acetone. The insoluble was removed with a line filter. Subsequently, 58.3 kg of water was added to the solution, to precipitate a crystalline product. The crystalline product was collected on a filter paper and washed with an acetone/water mixture, to give 19.5 kg of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine.

[Example 10] Preparation of 2-chloro-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine

In a 25 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 1.00 g (3.43 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine and 3.4 mL (3.7 mmol.) of phosphorus oxychloride. The mixture was heated to 100-106°C for 1.5 hours under refluxing, to carry out reaction. After the reaction was complete, the reaction mixture was cooled to room temperature, and poured into an ice/water mixture. The resulting aqueous mixture was neutralized with a saturated aqueous sodium hydrogen carbonate solution. The neutralized aqueous mixture was extracted with ethyl acetate. The ethyl acetate portion was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The dried ethyl acetate portion was filtered and concentrated under reduced pressure, to obtain 1.03 g of 2-chloro-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine as a colorless crystalline product having the below-mentioned characteristics. The yield was 97% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

m.p.: 99-101°C

UV λ_{max} (CH_3CN, nm): 194.7, 276.5

IR (KBr, cm^{-1}): 2980, 1728, 1542, 1508, 1227, 1086.

^{1}H-NMR (DMSO-d_6, δ(ppm)): 1.33 (6H, d, J=6.8Hz), 3.1-3.2 (1H, m), 3.76 (3H, s), 7.15 (2H, t, J=8.5Hz), 7.6-7.7 (2H, m).

HRMS: 308.0695 (theoretical value ($C_{15}H_{14}ClFN_2O_2$(M+)) 308.0728)

[Example 11] Preparation of 2-chloro-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine

In a 25 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 1.00 g (3.43 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-

isopropyl-5-methoxycarbonylpyrimidine, 0.5 mL (3.9 mmol.) of thionyl chloride, 3.44 mL of toluene, and 0.11 mL of N,N-dimethylformamide. The mixture was heated to 80°C for 3 hours, to carry out reaction. After the reaction was complete, the reaction mixture was cooled to room temperature, and poured into an ice/water mixture. The resulting aqueous mixture was neutralized with a saturated aqueous sodium hydrogen carbonate solution. The neutralized aqueous mixture was extracted with ethyl acetate. The ethyl acetate portion was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The dried ethyl acetate portion was filtered and concentrated under reduced pressure, to obtain 0.80 g of 2-chloro-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine as a colorless crystalline product. The yield was 76% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

[Example 12] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine

In a 25 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 546 mg (5 mmol.) of N-methylmethanesulfonamide, 551 mg (5 mmol.) of sodium t-pentoxide, 10 mL of acetonitrile, and 309 mg (1 mmol.) of 2-chloro-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine. The mixture was heated to 81-82°C for 3 hours under refluxing, to carry out reaction. After the reaction was complete, the reaction mixture was cooled to room temperature. To the cooled mixture was added 10 mL of water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate portion was separated, and dried over anhydrous magnesium sulfate. The dried ethyl acetate portion was filtered and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (column: Wako Gel C-200, eluent: hexane/ethyl acetate (2:1, volume ratio)). There was obtained 339 mg of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine. The yield was 89% (based on the amount of 2-chloro-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine).

[Example 13] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-methanesulfonyloxypyrimidine

In a 100 mL-volume glass flask were placed 10.0 g (34.4 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine, 5.22 g (58.5 mmol.) of triethylamine, and 34 mL of acetonitrile. The mixture in the flask was chilled to 0-5°C in an ice bath. To the chilled mixture was slowly added 5.12 g (44.7 mmol.) of methanesulfonyl chloride, and the resulting mixture was subjected to reaction at 20-25°C for 2 hours. After the reaction was complete, to the reaction mixture was added 60 mL of water. The aqueous reaction mixture was extracted with toluene and the toluene portion was separated. The toluene portion was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The dried mixture was filtered and concentrated under reduced pressure. The residue was crystallized from methanol, to give 11.3 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-methanesulfonyloxypyrimidine as a colorless crystalline product having the below-mentioned characteristics. The yield was 89% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

m.p.: 110-111°C

UV λ_{max} (CH_3CN, nm): 193.7, 276.8

IR (KBr, cm^{-1}): 2980, 1724, 1562, 1391, 1250, 1175, 1079, 971.

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.33 (6H, d, J=6.6Hz), 3.20 (1H, m), 3.60 (3H, s), 7.1-7.2 (2H, s), 7.6-7.8 (2H, m).

HRMS: 368.0842 (theoretical value ($C_{15}H_{17}FN_2O_5S$(M+)) 368.0892)

[Example 14] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-toluenesulfonyloxy)pyrimidine

In a 200 mL-volume glass flask were placed 27.6 g (95.1 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine, 12.5 g (123 mmol.) of triethylamine, and 95 mL of acetonitrile. The mixture of the flask was chilled to 0-5°C in an ice bath. To the chilled mixture was slowly added 20.0 g (105 mmol.) of p-toluenesulfonyl chloride, and the resulting mixture was subjected to reaction at 20-25°C for one hour. After the reaction was complete, to the reaction mixture was added 95 mL of water. The aqueous reaction mixture was extracted with toluene and the toluene portion was separated. The toluene portion was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The dried mixture was filtered and concentrated under reduced pressure. The residue was crystallized from methanol, to give 35.9 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-toluenesulfonyloxy)pyrimidine as a colorless crystalline product having the below-mentioned characteristics. The yield was 85% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

m.p.: 94-96°C

UV λ_{max} (CH_3CN, nm): 194.9, 275.2

IR (KBr, cm^{-1}): 2961, 1734, 1539, 1389, 1352, 1247, 1090, 980.

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.23 (6H, d, J=6.8Hz), 2.45 (3H, s), 3.0-3.2 (1H, m), 3.74

J=8.5Hz).

HRMS: 444.1155 (theoretical value ($C_{32}H_{21}FN_2O_5S$(M+)) 444.1194)

[Example 15] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-benzenesulfonyloxypyrimidine

The procedures of Example 13 were repeated except for replacing p-toluenesulfonyl chloride with 18.5 g (105 mmol.) of benzenesulfonyl chloride.

There was obtained 39.3 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-benzenesulfonyloxypyrimidine as a pale yellow crystalline product having the below-mentioned characteristics. The yield was 96% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.21 (6H, d, J=6.4Hz), 3.0-3.1 (1H, m), 3.73 (3H, s), 7.1-7.2 (2H, m), 7.5-7.7 (5H, m), 8.1-8.2 (2H, m).

[Example 16] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(2,4,6-trimethylbenzenesulfonyloxy)pyrimidine

The procedures of Example 13 were repeated except for replacing p-toluenesulfonyl chloride with 23.0 g (105 mmol.) of 2,4,6-trimethylbenzenesulfonyl chloride.

There was obtained 37.7 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(2,4,6-trimethylbenzenesulfonyloxy)pyrimidine as a pale yellow crystalline product having the below-mentioned characteristics. The yield was 84% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.17 (6H, d, J=6.8Hz),

2.34 (3H, s), 2.67 (6H, s), 3.0-3.1 (1H, m), 3.73 (3H, s), 7.00 (2H, s), 7.0-7.2 (2H, m), 7.4-7.5 (2H, m).

[Example 17] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(2,4,6-triisopropylbenzenesulfonyloxy)pyrimidine

The procedures of Example 13 were repeated except for replacing p-toluenesulfonyl chloride with 31.8 g (105 mmol.) of 2,4,6-triisopropylbenzenesulfonyl chloride.

There was obtained 47.1 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(2,4,6-triisopropylbenzenesulfonyloxy)pyrimidine as a pale yellow crystalline product having the below-mentioned characteristics. The yield was 89% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.12 (6H, d, J=6.6Hz), 1.19 (12H, d, J=6.8Hz), 1.27 (6H, d, J=7.1Hz), 2.8-2.95 (1H, m), 2.95-3.1 (1H, m), 3.73 (3H, s), 4.1-4.3 (2H, m), 7.0-7.1 (2H, m), 7.20 (2H, s), 7.4-7.5 (2H, m).

[Example 18] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-methoxybenzenesulfonyloxy)-pyrimidine

The procedures of Example 13 were repeated except for replacing p-toluenesulfonyl chloride with 21.7 g (105 mmol.) of p-methoxybenzenesulfonyl chloride.

There was obtained 39.9 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-methoxybenzenesulfonyloxy)pyrimidine as a colorless crystalline product having the below-mentioned characteristics. The yield was 91% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.25 (6H, d, J=6.8Hz), 3.0-3.2 (1H, m), 3.74 (3H, s), 3.88 (3H, s), 6.99 (2H, dd, J=2.0, 9.0Hz), 7.0-7.2 (2H, m), 7.5-7.7 (2H, m), 8.07 (2H, dd, J=2.2, 9.0Hz).

[Example 19] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-chlorobenzenesulfonyloxy)-pyrimidine

The procedures of Example 13 were repeated except for replacing p-toluenesulfonyl chloride with 22.2 g (105 mmol.) of p-chlorobenzenesulfonyl chloride.

There was obtained 39.9 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-chlorobenzenesulfonyloxy)pyrimidine as a colorless crystalline product having the below-mentioned characteristics. The yield was 89% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.23 (6H, d, J=6.6Hz), 3.0-3.2 (1H, m), 3.74 (3H, s), 7.1-7.2 (2H, m), 7.5-7.7 (4H, m), 8.0-8.1 (2H, m).

[Example 20] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(2-nitrobenzenesulfonyloxy)-pyrimidine

The procedures of Example 13 were repeated except for replacing p-toluenesulfonyl chloride with 23.3 g (105 mmol.) of 2-nitrobenzenesulfonyl chloride.

There was obtained 28.0 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(2-nitrobenzenesulfonyloxy)pyrimidine as an opaque crystalline product having the below-mentioned characteristics. The yield was 62% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.17 (6H, d, J=6.8Hz), 3.0-3.2 (1H, m), 3.75 (3H, s), 7.1-7.2 (2H, m), 7.5-7.6 (2H, m), 7.7-8.0 (3H, m), 8.33 (1H, dd, J=1.7, 8.1Hz).

[Example 21] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine

In a 25 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 196 mg (1.8 mmol.) of N-methylmethanesulfonamide, 198 mg (1.8 mmol.) of sodium t-pentoxide, 7.5 mL of acetonitrile, and 667 mg (1.5 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-toluenesulfonyloxy)pyrimidine. The mixture was heated to 81-82°C for 1.5 hours under refluxing, to carry out reaction. After the reaction was complete, the reaction mixture was cooled to room temperature. To the cooled mixture was added 10 mL of water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate portion was separated, and dried over anhydrous magnesium sulfate. The dried ethyl acetate portion was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (column: Wako Gel C-200, eluent: hexane/ethyl acetate (2:1, volume ratio)). There was obtained 428 mg of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidine. The yield was 75% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-toluenesulfonyloxy)pyrimidine).

[Example 22] Preparation of (2-amino-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine

In a 25 mL-volume glass flask equipped with a stirrer, a thermometer and a gas inlet were placed under ice-chilling 1.00 g (2.71 mmol.) of 4-(4-fluorophenyl)-6-iso-

propyl-5-methoxycarbonyl-2-methanesulfonyloxypyrimidine and 8.1 mL of tetrahydrofuran. The mixture was stirred at room temperature for 12 hours under gaseous ammonia atmosphere, for carrying out reaction. After the reaction was complete, 10 mL of water was added to the reaction mixture. The aqueuos mixture was then subjected to extraction with toluene. The toluene portion was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The dried toluene portion was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (column: Wako Gel C-200, eluent: hexane/ethyl acetate (2:1, volume ratio)). There was obtained 0.63 g of 2-amino-4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonylpyrimidine. The yield was 80% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-methanesulfonyloxypyrimidine).
6-isopropyl-5-methoxycarbonylpyrimidine

[Example 23] Preparation of (4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-N-methylaminopyrimidine

In a 50 mL-volume glass flask equipped with a stirrer, a thermometer and a dropping funnel was placed 6.00 g (16.3 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-methanesulfonyloxypyrimidine. Into the flask was slowly dropped under ice-chilling 5.06 g (65.2 mmol) of aqueous 40 wt.% methylamine solution. The resulting mixture was stirred for one hour at the same temperature for carrying out reaction. After the reaction was complete, 16 mL of water was added to the reaction mixture. The aqueuos mixture was then subjected to extraction with toluene. The toluene portion was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The dried toluene portion was filtered and concentrated under reduced pressure to give 4.81 g of 4-(4-fluorophenyl)-6-

isopropyl-5-methoxycarbonyl-2-N-methylaminopyrimidine. The yield was 97% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-methanesulfonyloxypyrimidine).

[Example 24] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-trifluoromethanesulfonyloxypyrimidine

In a 300 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 8.7 g (30.0 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine, 3.0 g (30.0 mmol.) of triethylamine, and 150 mL of toluene. The mixture in the flask was chilled to 0°C in an ice bath. To the chilled mixture was slowly added 8.46 g (30.0 mmol.) of trifluoromethanesulfonic anhydride, and the resulting mixture was subjected to reaction for 3 hours at the same temperature. After the reaction was complete, to the reaction mixture was added 90 mL of water. From the aqueous reaction mixture, an organic liquid portion was separated. The organic liquid portion was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (column: Wako Gel C-200, eluent: hexane/ ethyl acetate (8:2, volume ratio)). There was obtained 8.46 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-trifluoromethanesulfonyloxypyrimidine having the below-mentioned characteristics as a colorless oil. The yield was 74% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

IR (KBr, cm^{-1}): 3421, 2978, 1737, 1570, 1429, 1222, 1136, 973, 851

^{1}H-NMR ($CDCl_3$, δ(ppm)): 1.33 (6H, d, J=6.6Hz), 3.1-3.2(1H, m), 3.80 (3H, s), 7.1-7.2 (2H, m), 7.7-7.8 (2H, m)

HRMS: 422.0585 (theoretical value ($C_{16}H_{14}F_4N_2O_5S$(M+)) 422.0560)

[Example 25] Preparation of 4-(4-flurophenyl)-6-isopropyl-5-methoxycarbonyl-2-trifluoromethanesulfonyloxypyrimidine

In a 300 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 2.9 g (10.0 mmol.) of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine, 1.7 g (16.8 mmol.) of triethylamine, and 50 mL of toluene. The mixture in the flask was chilled to 0°C in an ice bath. To the chilled mixture was slowly added 2.4 g (14.1 mmol.) of trifluoromethanesulfonyl chloride, and the resulting mixture was subjected to reaction for 3 hours at the same temperature. After the reaction was complete, to the reaction mixture was added 30 mL of water. From the aqueous reaction mixture, an organic liquid portion was separated. The organic liquid portion was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (column: Wako Gel C-200, eluent: hexane/ethyl acetate (8:2, volume ratio)). There was obtained 2.8 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-trifluoromethanesulfonyloxypyrimidine having the below-mentioned characteristics as a colorless oil. The yield was 66% (based on the amount of 4-(4-fluorophenyl)-2-hydroxy-6-isopropyl-5-methoxycarbonylpyrimidine).

[Example 26] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine

In a 50 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 3.0 g (7 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-trifluoromethanesulfonyloxypyrimidine, 1.45 g

(10.5 mmol.) of potassium carbonate (available from Wako Junyaku Co., Ltd., special grade), and 14 mL of butyl acetate. The mixture was heated to 122-125°C for 3 hours under refluxing, to carry out reaction. After the reaction was complete, the reaction mixture was cooled to room temperature. To the reaction mixture were added 10 mL of water and 7 mL of acetone, and the organic liquid portion was separated. The organic liquid portion was washed with a saturated aqueous sodium chloride solution and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (column: Wako Gel C-200, eluent: hexane/ ethyl acetate (5:1, volume ratio)). There was obtained 2.1 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine as a white crystalline product. The yield was 78% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-trifluoromethanesulfonyloxypyrimidine).

[Example 27] Preparation of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine

In a 50 mL-volume glass flask equipped with a stirrer, a thermometer and a reflux condenser were placed 1.1 g (2.5 mmol.) of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-toluenesulfonyloxy)pyrimidine, 0.55 g (5.0 mmol.) of N-methylmethanesulfonamide, 0.69 g (5.0 mmol.) of potassium carbonate (available from Wako Junyaku Co., Ltd., special grade), 0.32 g (1.0 mmol.) of tetrabutylammonium bromide, 20 mL of toluene and 5 mL of water. The mixture was heated to 85°C for 28 hours under refluxing, to carry out reaction. After the reaction was complete, the reaction mixture was cooled to room temperature. To the reaction mixture were added 10 mL of water and 7 mL of acetone, and the organic liquid portion was separated. The organic liquid portion was analyzed by

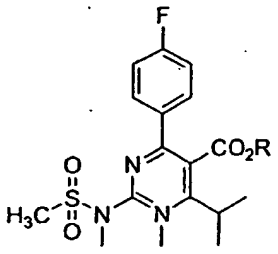
high performance liquid chromatography. It was confirmed that 0.6 g of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(N-methyl-N-methanesulfonylamino)pyrimidine was produced. The yield was 63% (based on the amount of 4-(4-fluorophenyl)-6-isopropyl-5-methoxycarbonyl-2-(p-toluenesulfonyloxy)pyrimidine).

[Industrial Utility]

The pyrimidine compound, particularly, 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound, prepared by the invention is of value as an intermediate compound for the production of a cholesterol reducing agent (HMG-CoA reductase agent). The compound of formula (3) can be converted to an HMG CoA reductase inhibitor by the processes disclosed in European Patent Application Publication No. 0521471, Bioorg. Med. Chem., 5, 437 (1997) and International Patent Application No. WO 00/49014. The disclosures of these references are incorporated herein by reference to demonstrate how a compound of formula (3) or formula (8) can be converted to an HMG CoA reductase inhibitor, in particular, rosuvastatin or a pharmaceutically acceptable salt thereof, such as rosuvastatin calcium.

CLAIMS

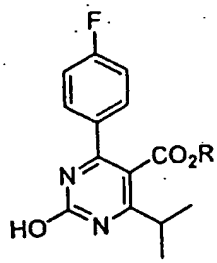
1. A process for preparing a 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound having the formula (3):



(3)

in which R is a hydrocarbyl group,
which comprises the steps of:

reacting a hydroxypyrimidine compound having the formula (1):



(1)

in which R is the same as above,
with an organic sulfonyl halide having the formula (2):

$$R'SO_2X \qquad (2)$$

in which R' is a hydrocarbyl group and X is a halogen atom, or an organic sulfonic anhydride having the formula (2a):

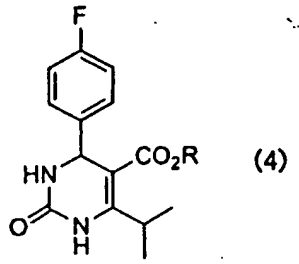
$$(R'SO_2)_2O \qquad (2a)$$

in which R' has the same meaning as above, and

reacting the resulting reaction product with N-methyl-N-methanesulfonamide.

2. The process of claim 1, wherein both of the reaction of the hydroxypyrimidine compound with the organic sulfonyl halide or the organic sulfonic anhydride and the reaction of the resulting reaction product with N-methyl-N-methanesulfonamide are performed in the presence of a base.

3. The process of claim 1, wherein the hydroxypyrimidine compound is prepared by oxidizing a dihydropyrimidinone compound having the formula (4):

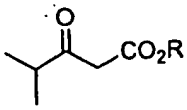


(4)

wherein R is the same as defined in claim 1.

4. The process of claim 3, wherein the dihydropyrimidinone compound is oxidized using nitric acid.

5. The process of claim 3, wherein the dihydropyrimidinone compound is prepared by reacting an isobutyrylacetate ester having the formula (5):



(5)

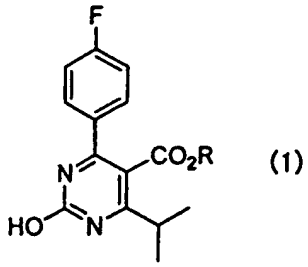
in which R is the same as defined in claim 1,
with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt.

6. The process of claim 5, wherein the protonic compound is a protonic acid.

7. The process of claim 6, wherein the protonic acid is sulfuric acid.

8. The process of claim 5, wherein the metal salt is copper(I) chloride.

9. A hydroxypyrimidine compound having the formula (1):

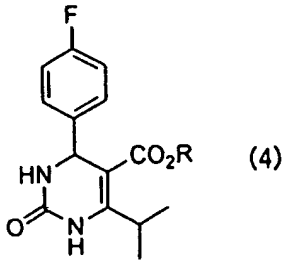


(1)

in which R is a hydrocarbyl group.

10. The hydroxypyrimidine compound of claim 9, wherein R is an alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, an aryl-alkyl group having an alkyl moiety of 1-3 carbon atoms, or an aryl group.

11. A method for preparing the hydroxypyrimidine compound of claim 9, which comprises oxidizing a dihydro-pyrimidinone compound having the formula (4):

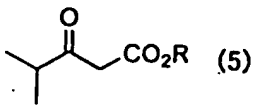


(4)

wherein R is a hydrocarbyl group.

12. The method of claim 11, wherein the dihydro-pyrimidinone compound is oxidized using nitric acid.

13. The method of claim 11, wherein the dihydropyrimidinone compound is prepared by reacting an isobutyrylacetate ester having the formula (5):



(5)

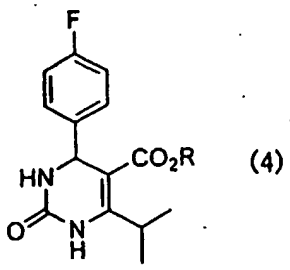
in which R is the same as defined in claim 11, with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt.

14. The method of claim 13, wherein the protonic compound is a protonic acid.

15. The method of claim 14, wherein the protonic acid is sulfuric acid.

16. The method of claim 13, wherein the metal salt is copper(I) chloride.

17. A dihydropyrimidinone compound having the formula (4):

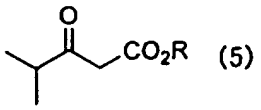


(4)

wherein R is a hydrocarbyl group.

18. The hydroxypyrimidinone compound of claim 17, wherein R is an alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, an arylalkyl group having an alkyl moiety of 1-3 carbon atoms, or an aryl group.

19. A method for preparing the dihydropyrimidinone compound of claim 17, which comprises reacting an isobutyrylacetate ester having the formula (5):



(5)

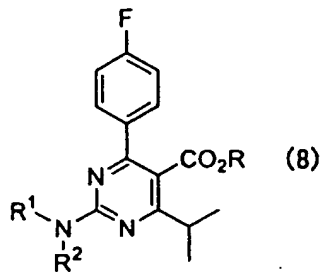
in which R is the same as defined in claim 17, with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt.

20. The method of claim 19, wherein the protonic compound is a protonic acid.

21. The method of claim 19, wherein the protonic acid is sulfuric acid.

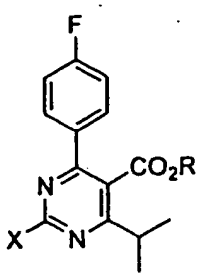
22. The method of claim 19, wherein the metal salt is copper(I) chloride.

23. A method for preparing an aminopyrimidine compound having the formula (8):



(8)

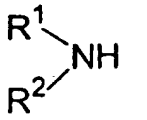
wherein R is a hydrocarbyl group, and each of R^1 and R^2 independently is hydrogen atom, an alkyl group, an alkylsulfonyl group, or an arylsulfonyl group, which comprises reacting a 2-substituted pyrimidine compound having the formula (6):



(6)

wherein R is the same as above, and X is a halogen atom or an organic sulfonyloxy group,

with an amine compound having the formula (7):



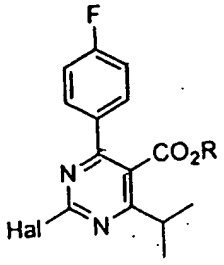
(7)

wherein each of R^1 and R^2 is the same as above.

24. The method of claim 23, wherein R^1 is methyl and R^2 is methanesulfonyl.

25. The method of claim 23, wherein the reaction of the 2-substituted pyrimidine compound with the amine compound is performed in the presence of a base.

26. A halogenopyrimidine compound having the formula (9):



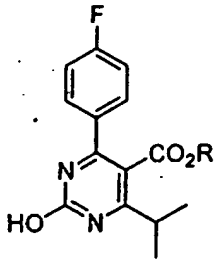
(9)

wherein R is a hydrocarbyl group, and Hal is a halogen atom.

27. The halogenopyrimidine compound of claim 26, wherein R is an alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, an arylalkyl group having an alkyl moiety of 1-3 carbon atoms, or an aryl group.

28. The halogenopyrimidine compound of claim 26, wherein Hal is a chlorine atom.

29. A method for preparing the halogenopyrimidine compound of claim 26, which comprises reacting a hydroxypyrimidine compound having the formula (1):

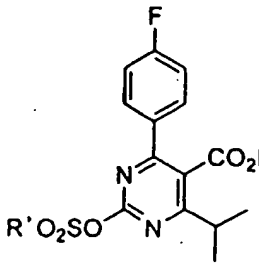


(1)

wherein R is a hydrocarbyl group,
with a halogenating agent.

30. The method of claim 29, wherein the halogenating agent is phosphorus oxychloride or thionyl chloride.

31. An organic sulfonyloxypyrimidine compound having the formula (10):

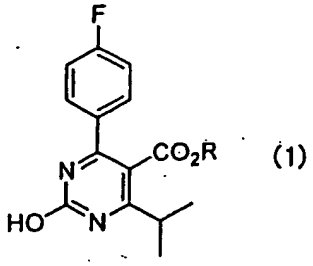


(10)

wherein each of R and R' independently is a hydrocarbyl group.

32. The organic sulfonyloxypyrimidine compound of claim 31, wherein each of R and R' independently is an alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, an arylalkyl group having an alkyl moiety of 1-3 carbon atoms, or an aryl group.

33. A method for preparing the organic sulfonyloxypyrimidine compound of claim 31, which comprises reacting a hydroxypyrimidine compound having the formula (1):



(1)

wherein R is a hydrocarbyl group,
with an organic sulfonyl halide having the formula (2):

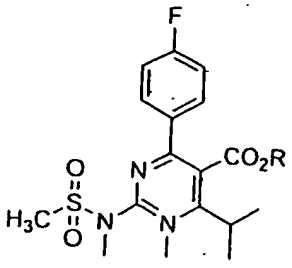
$$R'SO_2X \qquad (2)$$

wherein R' is a hydrocarbyl group, and X is a halogen atom, or an organic sulfonic anhydride having the formula (2a):

$$(R'SO_2)_2O \qquad (2a)$$

in which R' has the same meaning as above.

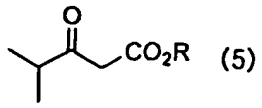
34. A process for preparing a 2-(N-methyl-N-methanesulfonylamino)pyrimidine compound having the formula (3):



(3)

in which R is a hydrocarbyl group,
which comprises the steps of:

(I) reacting an isobutyrylacetate ester of the following formula (5):



(5)

wherein R is a hydrocarbyl group.
with 4-fluorobenzaldehyde and urea in the presence of a protonic compound and a metal salt;

(II) oxidizing the reaction product of the step (I);

(III) reacting the oxidation product of the step (II) with an organic sulfonyl halide having the formula (2):

$$R'SO_2X \qquad (2)$$

in which R' is a hydrocarbyl group, and X is a halogen atom, or an organic sulfonic anhydride having the formula (2a):

$$(R'SO_2)_2O \qquad (2a)$$

in which R' has the same meaning as above; and

(IV) reacting the reaction product of the step (III) with N-methyl-N-methanesulfonamide.

35. The process of claim 1, wherein R' is a substituted or unsubstituted aryl group.

36. The process as claimed in claim 1, followed by conversion of the compound of formula (3) to rosuvastatin or a pharmaceutically acceptable salt thereof.

37. The process as claimed in claim 34, followed by conversion of the compound of formula (3) to rosuvastatin or a pharmaceutically acceptable salt thereof.

38. The method as claimed in claim 23, followed by conversion of the compound of formula (8) to an HMG CoA reductase inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/07129

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl⁷ C07D239/42,239/22,239/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl⁷ C07D239/42,239/22,239/34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN),REGISTRY(STN),WPIDS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 5-178841 A(Shionogi and Co.,LTD)1993.07.20 WHOLE DOCUMENT & EP 521471 A	1-38
A	Ma, Yun; Qian, Changtao; Wang, Limin; Yang, Min, Lanthanide Triflate Catalyzed Biginelli Reaction. One-Pot Synthesis of Dihydropyrimidinones under Solvent-Free Conditions, Journal of Organic Chemistry (2000), 65(12), 3864-3868	19-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
19.08.02

Date of mailing of the international search report
03.09.02

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